4 – ^{t}BUTYL IODOXYBENZENE : AN EFFECTIVE OZONE EQUIVALENT

A Thesis Submitted
In Partial Fulfilment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

SHIO KUMAR SINGH

to the

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR

JANUARY, 1987

In

Loving Memory of

My Grandfather

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Professor S. Ranganathan.

In keeping with the general practice of reporting scientific observations due acknowledgements have been made wherever the work embodied is based on the findings of other investigators.

Shio Kumar Singh

SHIO KUMAR SINGH

CERTIFICATE

Certified that the work contained in this thesis, entitled, "4-^{t}BUTYL IODOXYBENZENE: AN EFFECTIVE OZONE EQUIVALENT" has been carried out by Mr. Shio Kumar Singh, under my supervision and the same has not been submitted elsewhere for a degree.

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Thesis Supervisor

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January 1987.

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CERTIFICATE OF COURSE WORK

This is to certify that Mr. Shio Kumar Singh has satisfactorily completed all the course requirements for the Ph.D. degree programme. The courses include:

Chm 500	Basic Course in Mathematics
Chm 501	Advanced Organic Chemistry I
Chm 502	Advanced Organic Chemistry II
Chm 524	Modern Physical Methods in Chemistry
Chm 542	Advanced Inorganic Chemistry II
Chm 581	Basic Biological Chemistry
Chm 800	General Seminar
Chm 801	Graduate Seminar
Chm 900	Research

Mr. Shio Kumar Singh has successfully completed his Ph.D. Qualifying Examinations in August 1982. Also he has successfully completed his open seminar of the work embodied in this thesis.

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My thanks are due to Master Anand, the ever smiling boy, whose presence in the lab made life homely and memorable.

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Finally, I wish to express my indebtedness and gratitude to my parents, brothers, sisters and in-laws for their constant support and encouragement which made me what I am today.

SHIO KUMAR SINGH

PREFACE

ORGANIZATION

This thesis entitled, "4-^{t}Butyl Iodoxybenzene - An Effective Ozone Equivalent" consists of six parts, namely, A. Introduction, B. Background, C. Present work, D. Spectra, E. Experimental, and F. References.

SUMMARY OF THE PRESENT WORK

The genesis of the work reported in the present thesis arises from an analysis of reactions which, whilst allowed by the Woodward-Hoffmann rules, do not take place. While these rules predict the allowedness or otherwise of a particular reaction, they do not specify whether kinetic or thermodynamic barriers would permit the occurrence of such a reaction. An analysis of a large variety of such reactions carried out in the present laboratory, some time ago, led to interest in the nitro group as a possible ozone equivalent. In complete contrast to the high reactivity of ozone to π systems, the isoelectronic nitro group is inert to these functions. Various considerations have led to the conclusion that the exceptionally high heat of formation of ozone (+34 kcal mol^{-1}) is a major reason for its reactivity. This analysis also showed that the modest unfavourable activation energy associated with a hypothetical addition of nitrobenzene to π systems could be overcome by perturbation of this molecule with electron withdrawing substituents. A modest amount of success was obtained in the

study of variously perturbed nitrobenzenes as possible ozone equivalents. However, solubility and reactivity considerations set a limit towards the use of perturbed nitro aromatics as ozone equivalents and suggested that an equivalent but entirely different system, which could have enhanced reactivity should be explored. Iodoxybenzene, possessing a functional group that is isoelectronic to ozone and nitro group, can be expected to have a substantially positive heat of formation and additionally, the highly polarized I-O bond in this compound can be anticipated to reduce the kinetic activation energy barrier. In the event, iodoxybenzene turned out to be a reagent of promise and exhibited properties remarkably parallel to that of ozone. A severe drawback of iodoxybenzene utility was that it was practically insoluble in most solvents, thus preventing its wide use in chemical reactions. It was felt that this serious impediment could be overcome by attachment of hydrophobic residue to the aromatic moiety. Such investigations have led to the synthesis of 4-^{t}butyl iodoxybenzene and its demonstration as a practical and reliable ozone equivalent. The thrust of the present work is then to assess the utility of this reagent so that it could be used with confidence in organic synthetic operations.

The title reagent, 4-^{t}butyl iodoxybenzene (1)* was prepared from t-butyl benzene *via* iodination with HIO_3-I_2, trans-

*The numbers shown refer to those presented in the thesis, Sections C and E.

formation to 4-^{t}butylbenzene iodinedichloride (3) with Cl_2 and treatment with elements of HOCl.

Thus, 4-^{t}butyl iodoxybenzene can be prepared in excellent yields from readily available materials. It is a stable compound and its solubility compared to the parent is substantial. The estimated solubility of (1) in hot benzene, chlorobenzene and nitrobenzene are respectively 0.2%, 6% and 9%.

In the present work, 4-^{t}butyl iodoxybenzene (1) has been demonstrated to be an excellent oxygen transfer reagent in the sense that the reaction of (1) with various substrates leads to nearly total recovery of 4-^{t}butyl iodobenzene (2), which could be recycled. The transformations brought about with 4-^{t}butyl iodoxybenzene are clean, the products readily isolable and the resulting (2) effectively recycled.

The present work has shown that the reaction profile of (1) could be understood in terms of five broad types.

In Type I reactions, reagent (1) shows a profile remarkably similar to that of ozone, namely the cleavage of π bonds to carbonyl compound. The following transformations have been carried out to illustrate the potential of (1) as an ozone equivalent: biscyclohexylidine $\rightarrow$ cyclohexanone (59%), E-stilbene $\rightarrow$ benzaldehyde (67%) + benzil (20%), 9-benzylidinefluorene $\rightarrow$ fluorenone (50%) + benzaldehyde (45%), diphenylacetylene $\rightarrow$ benzil (66%) and camphene $\rightarrow$ camphenilinone (50%).

Type II reactions brought about by (1) involve the effective transformations of π systems possessing vicinal hydrogens to 1,2-diketones. An excellent example of this is the transformation of phenanthrene to phenanthrenequinone in excellent yield.

Type III reactions brought about by reagent (1) are initiated by an electrophilic attack of the reagent at peripositions of condensed aromatic systems, eventually leading to quinones. This aspect has been illustrated with the transformation of anthracene ⟶ anthraquinone in 59% yield.

Type IV reactions of (1) are also similar to that of ozone, namely the proclivity to insert into aralkyl C-H bonds. This has been taken advantage of, in the illustration of a practical and convenient route to α-tetralone by reaction with (1).

To type V reactions belong the transformation of aromatic amines to azo compounds in good yields. This aspect has been illustrated in the present work primarily with the aniline ⟶ azo benzene conversion. Aralkyl amines interestingly are oxidized to aldehydes and as illustrated with a transformation of benzylamine to benzaldehyde.

The scope of reagent (1) in bringing about oxidative transformations of coded α-amino acids side chains have been examined with the objective of utilizing this reagent to bring

about the side specific and group specific transformations of such side chains in amino acids and proteins.

N-Benzoyl-L-methionine methyl ester (4) on treatment with reagent (1) gave a multitude of products, which were carefully separated and their structures established. This reaction gave the expected sulfone (5, 29%), sulfoxide (6, 36%) and, in addition, the sulfenic acid (7, 11%), its methyl ester (9, 12%) and N-benzoyl-L-aspartic acid dimethyl ester (8, 7%). It is envisaged that the primary pathway is the transformation of (4) to the sulfone (5) and sulfoxide (6) by oxygen transfer from the reagent (1). The sulfoxide (6) is transformed to the sulfenic acid (7) by a Type III reaction of reagent (1). The formation of aspartic acid is rationalized again on the basis of type III reaction brought about with 1 followed by a loss of elements of $MeSO_2H$.

The smooth transformation of N-benzyloxycarbonyl-L-methionine methyl ester (13) to the corresponding sulfone (14, 57%) illustrate the preferential oxidation of the sulfur to the aromatic moiety that is present as the protecting group. Surprisingly the reaction also afforded benzylcarbamate (15, 36%) arising from elimination.

The dipeptide N-benzyloxycarbonyl glycyl-L-methionine methyl ester (17) gave the sulfone (18, 26%) and the sulfoxide (19, 42%), on treatment with (1), thus showing that the peptide

linkage is not affected in oxidations mediated with reagent (1).

N-Benzyloxycarbonyl-S-benzyl-L-cysteine methyl ester (20) on treatment with (1) gave the sulfone (21 18%) and the sulfoxide (22, 30%). In addition, the azlactone (23) arising from the sulfoxide (22) was isolated in 8% yields.

A surprising observation was the efficiency with which the reagent (1) transformed N-benzoyl-L-serine methyl ester (25) to the corresponding dehydro alanine (26) in 55% yields. Blank reactions showed that the elimination is effected by interaction with (1). The reaction also gave the alternate product of elimination, namely benzamide. The formation of (26) as well as benzamide could be understood in terms of eliminations proceeding through six membered transition state from the primary adduct of (25) with (1).

The transformation of N-benzoyl-L-phenylalanine methyl ester (27) to N-benzoyl-L-aspartic acid dimethyl ester (8) in 14% yield is significant in the sense that it not only demonstrates the ability of reagent (1) like ozone to oxidise aromatic rings to a carboxyl unit, but also that in such systems the phenyl of the benzoyl protecting group does not suffer reaction with (1).

N-Benzyloxycarbonyl-L-histidine methyl ester (28) on treatment with 1 gave as the substantial product N-benzyloxy-

The formation of (29) can be understood in terms of hydroxylation of the 4 position of the imidazole moiety present in (28) followed by prototropic shifts and hydrolytic cleavage.

A remarkable and practical reaction encountered in the present work was the transformation of N-benzoyl-L-tryptophan methyl ester (30) to the corresponding Kynurenine (31) in 70% yields. In this reaction the reagent (1) behaves precisely as ozone and with greater effectiveness.

N-Benzoyl-L-proline methyl ester (32) is oxidized to a pyroglutamic acid, the latter as expected, under conditions of workup, undergoes hydrolysis leading to N-benzoylglutamic acid α-methyl ester. This method could be further developed into useful procedure for changing the conformations of peptides *via* oxidation of proline residues to glutamic acids.

In addition, the reaction of 1 with unprotected amino acids such as phenylalanine methyl ester and tryptophan methyl ester were examined. These reactions gave unusual oxidation products.

Related to the present work is the development of a very effective method for the preparation of 2-nitroethyl phenyl sulfoxide (41) a recognized reagent for the efficient generation of nitroethylene *via* a Cope type of elimination. In the present work not only the reagent (1) has been effectively used in oxidation of 2-nitroethyl phenyl sulfide (42) to (41) without

effecting other functionalities but also the preparation of compound (42) was achieved in a novel manner from 2-bromo ethyl phenyl sulfide (43) with sodium nitrite in DMSO, thus obviating the use of nitromethane, hitherto invariably used for the preparation of nitroethylene, since, procedures starting from nitromethane are hazardous and poorly efficient. The procedure for the preparation of the transfer reagent 2-nitroethyl phenyl sulfoxide (41) was developed as a result of studies of the reaction of 2-bromoethyl phenyl sulfide (43) and 2-chloroethyl phenyl sulfide (45) with sodium nitrite and silver nitrite under various reaction conditions. While sodium nitrite in DMF or DMSO yielded, only the desired nitrocompound (41), the reagent silver nitrite gave a mixture of (42) and the corresponding nitrite (44).

<u>CONTENTS</u>

A. INTRODUCTION

The thesis entitled, "4-^{t}butyl iodoxybenzene - an effective ozone equivalent", has its focus, the preparation and study of the range of utility and applications of 4-^{t}butyl iodoxybenzene. In the recent years, there has been a justifiable resurgence of interest in hypervalent iodine compounds and their utility as reagents of choice for bringing about a variety of transformation is being increasingly recognised. It was felt that a brief summary pertaining to the reactions of hypervalent iodine compounds would form an appropriate background to the present work. Such a review is presented in the following section.

B. BACKGROUND

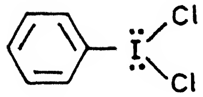
Excellent reviews have appeared recently outlining the properties of hypervalent iodine compounds.[1] The summary presented in this section endevours to present, in one place, an account of the reactions of the hypervalent iodine compounds, namely, phenyl iododichloride, diacetoxy iodobenzene, iodosobenzene and iodoxy benzene. This account is designed to provide a profile of such reagents and would be a supplement to the reviews referred to above.

I. Reactions of Phenyl iododichloride

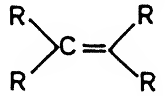
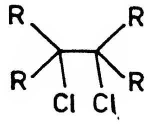
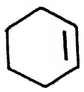
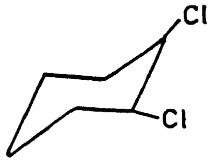
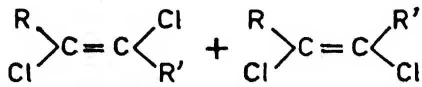
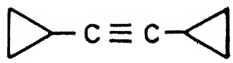
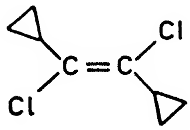
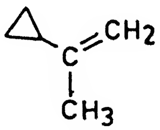
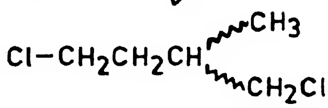
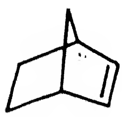
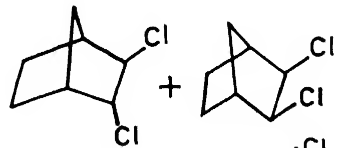
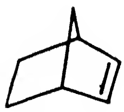
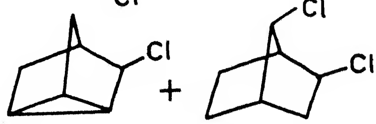
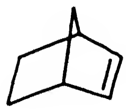
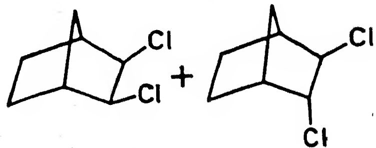
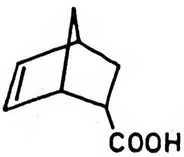
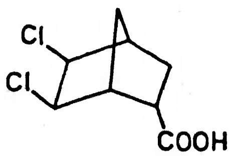
The most characteristic property of phenyl iododichloride, which can be easily prepared by reaction of iodobenzene with chlorine, is its ability to perform as an excellent chlorine transfer reagent. This is readily apparent from TABLE B.1, which outlines the reactivity of this reagent to diverse types of olefinic functions resulting in the net transfer of both the chlorines.[1] As could be expected, the addition is trans. The chlorine transfer could be understood as taking place in two steps, the primary one being the transfer of elements of Cl^+ to the π system to form a chloronium type intermediate, which would then undergo opening with Cl^- supplied by the reagent (CHART B.1).

TABLE B.1

REACTION TYPE

X +  → Z

Y

X	Y	Z	Ref.
 R = alkyl, aryl	Y		1
	Y		2
R − C ≡ C − R'	Y		3
	Y		4
	Y		5
	Y / hν		1
	Y / O_2		1
	Y		6
	Y		7

CONTD.

TABLE B.1

REACTION TYPE (CONTD.)

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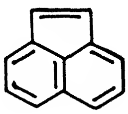
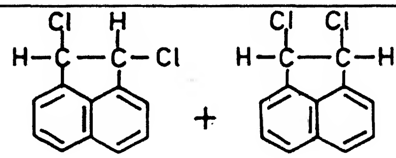
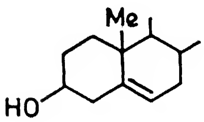
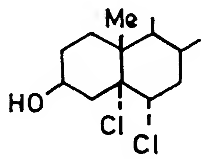
	Y		8
	Y		9

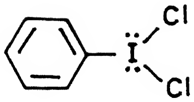
The intermediacy of the chloronium ion in chlorine transfer from phenyl iododichloride is best supported by reaction of 2-cyclopropyl propene. In this case, the cyclopropane rupture is a result of interaction with the chloronium ion intermediate, ultimately leading to the expected rearranged product.[5]

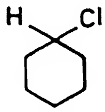
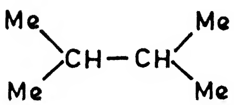
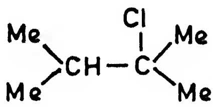
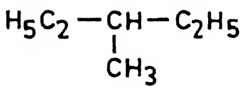
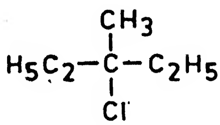
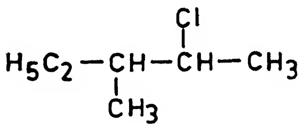
As shown in TABLE B.1, a variety of olefins readily undergo reaction with $PhICl_2$ leading to the dichloro systems. As could be expected, in the case of strained π systems such as those present in acenaphthylene and bicyclo[2.2.1]heptene, both the cis and the trans dichloro compounds are obtained.[1,6-8] The intermediacy of a chloronium ion becomes apparent in the reaction of this reagent with bicyclo[2.2.1]heptene leading to the formation of the expected rearranged product and the chlorotricycline.[1] An interesting aspect of phenyl iododichloride is that acetylenes react with this reagent leading to the trans- as well as cis-dichloro olefins. It appears that these products are resistant to further addition of halogen by the reagent.[3,4]

An important reaction of phenyl iododichloride that has been taken advantage of in organic synthesis (vide infra), is the monochlorination of hydrocarbon substrates. This is illustrated in TABLE B.2. Thus, cyclohexane, 2,3-dimethylbutane and 3-methylpentane undergo monohalogenation on treatment with the reagent under photochemical conditions. However, whilst in the case of cyclohexane[10] and 2,3-methyl-n-butane the

TABLE B.2

REACTION TYPE

X +  → Z

X	Y	Z	Ref.
	Y / hν		10
	-Y, hν/$B(C_6H_{13})_3$		11
	,,	 + 	11

chlorination takes place in the expected manner without rearrangement, in the case of 3-methylpentane the reaction is not so selective leading to halogenation of the tertiary as well as the secondary carbon atoms.[11] An interesting aspect of this halogenation is that it has been found that tri-n-hexylborane promotes this reaction.[11] The overall process could be envisaged as taking place precisely along the lines of the radical chlorination. Under photochemical conditions, the reagent breaks down to $PhICl^{\bullet}$ and $Cl^{\bullet}$. The $Cl^{\bullet}$ then abstracts a hydrogen from substrate and resulting $C^{\bullet}$ interacts with $PhICl^{\bullet}$ leading to the product (CHART B.2).

The tertiary halide arising from primary halogenation involving $PhICl_2$ under photochemical conditions could be transformed to the olefins <u>via</u> elimination of the halogen, either with Ag^+ or nucleophiles. This aspect has been taken advantage of for the synthesis of steroidal olefins.[12] Of particular interest, is the ingenious application of halogenation with $PhICl_2$ followed by elimination for remote functionalization at predetermined sites <u>via</u> tailor made reagents. This aspect is illustrated in TABLE B.3, which shows that the placement of the reagent using the 3-hydroxyl handle could lead to preferential formation of the desired π bond in the steroidal framework.[13,14]

Secondary alcohols are transformed to ketones using phenyl iododichloride in presence of a base.[15] This trans-

CHART B.1

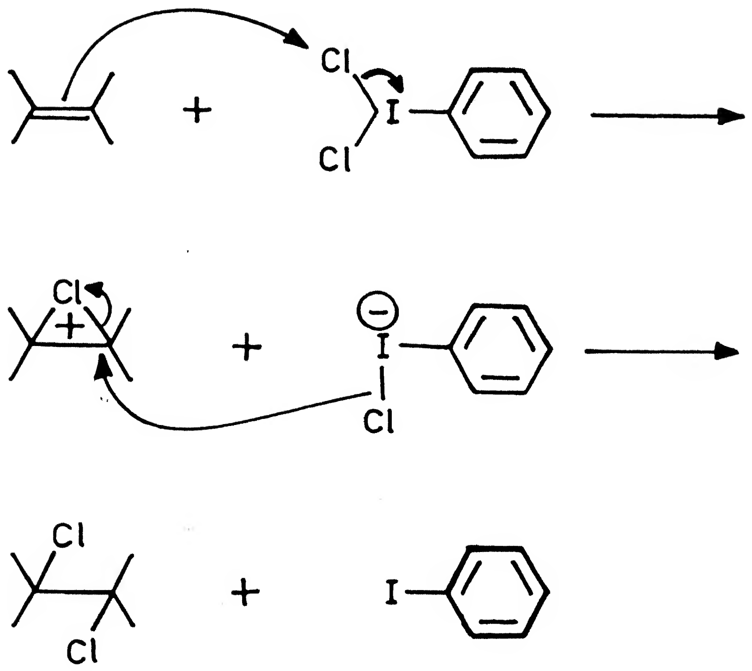


CHART B.2

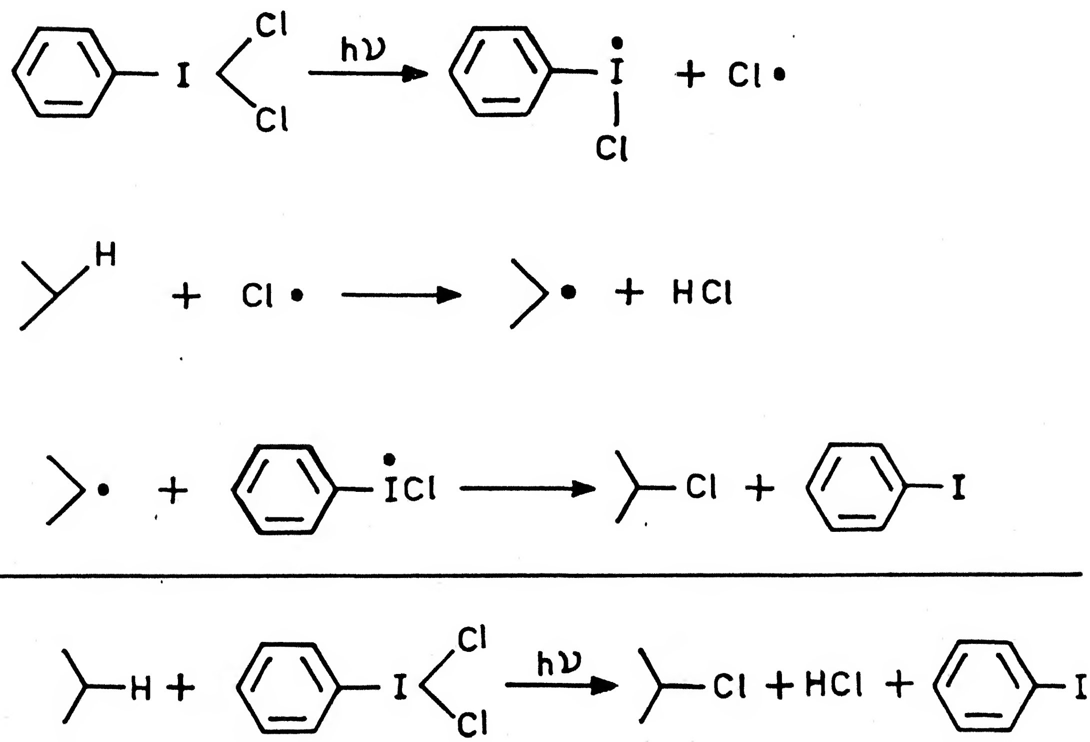
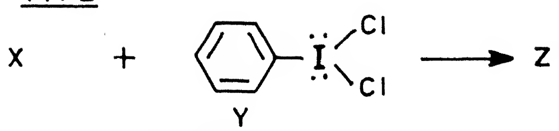


TABLE B.3

REACTION TYPE



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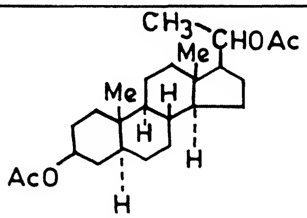
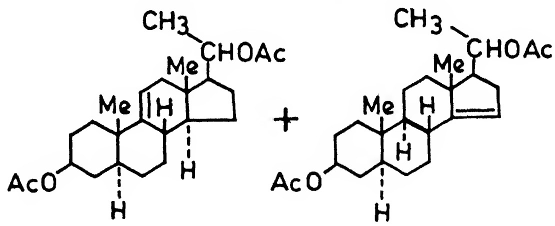
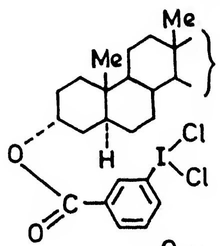
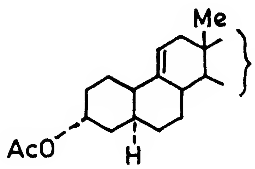
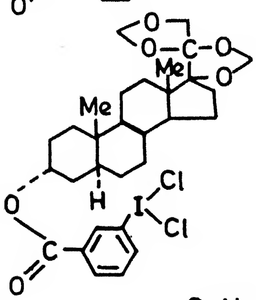
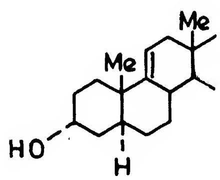
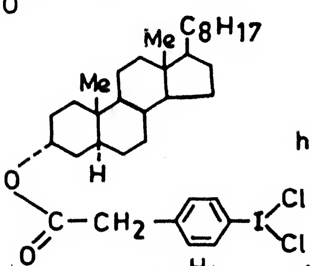
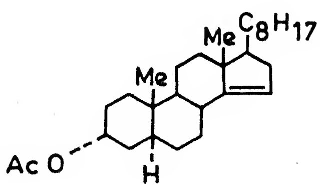
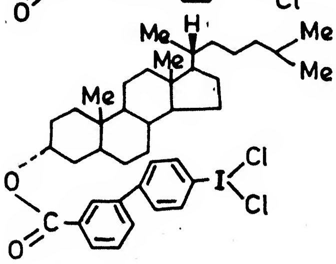
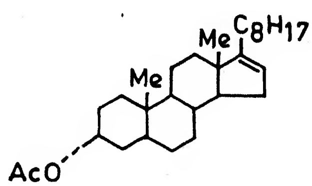
	Y, hν/$AgClO_4$		12
	hν/OH^-, Ac_2O		13
	hν		13
	hν, OH^-, Ac_2O		13
	OH^-, Ac_2O		14

formation can be best rationalised on the basis of initial displacement of Cl^- from the reagent leading to a substrate reagent intermediate which collapses to, in the presence of base, the ketone and iodobenzene (CHART B.3, TABLE B.4).

An interesting transformation mediated by phenyl iododichloride is the transformation of benzoin to benzil.[41] In this case, the benzoin was treated with two equivalents of sodium hydride. The formation of benzil under these conditions can be best explained as shown in CHART B.4. Finally, the reaction of phenyl iododichloride with some unusual substrates are listed in TABLE B.5.

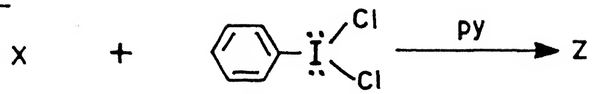
II. Reactions of Iodosobenzene

Today, amongst the hypervalent iodine compounds, iodosobenzene has stood out as a very versatile reagent, in the sense that this reagent has been demonstrated to bring about efficiently a variety of transformations. These are presented below.

The transformation of diverse π systems to their oxides with iodosobenzene, perhaps is the well studied reaction of this reagent. The reaction can be considered as taking place <u>via</u> interaction of the π system with the iodosyl oxygen followed by collapse to iodobenzene and the epoxide (CHART B.5). The epoxidation is generally promoted by iron porphyrins, although manganese porphyrins and copper salts have been effectively

TABLE B.4

REACTION TYPE



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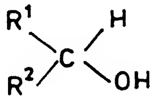
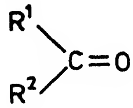
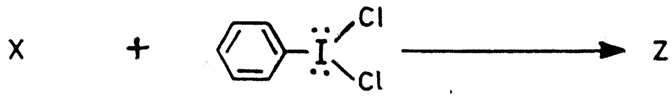
		15
5α – cholestan – 3α – ol	5α – cholestan – 3 – one	15

TABLE B.5

REACTION TYPE



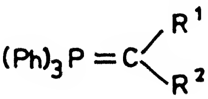
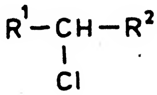
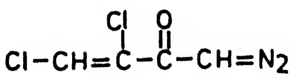
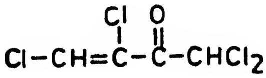
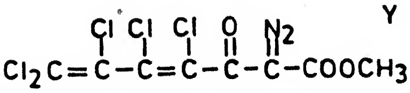
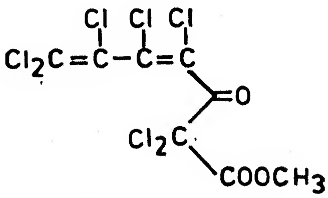
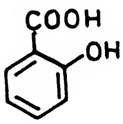
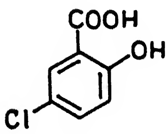
X	Y	Z	Ref.
 R^1 = alkyl, R^2 = acyl	Y, OH^-		16
	Y		17
	Y		17
	Y		18

CHART B.3

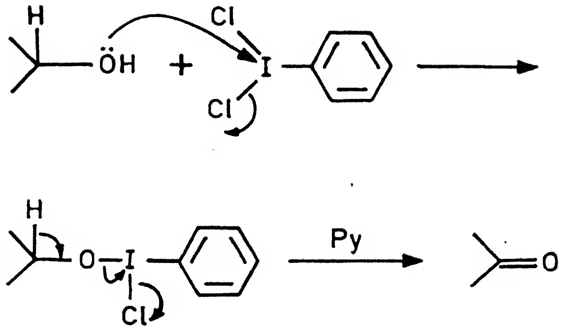


CHART B.4

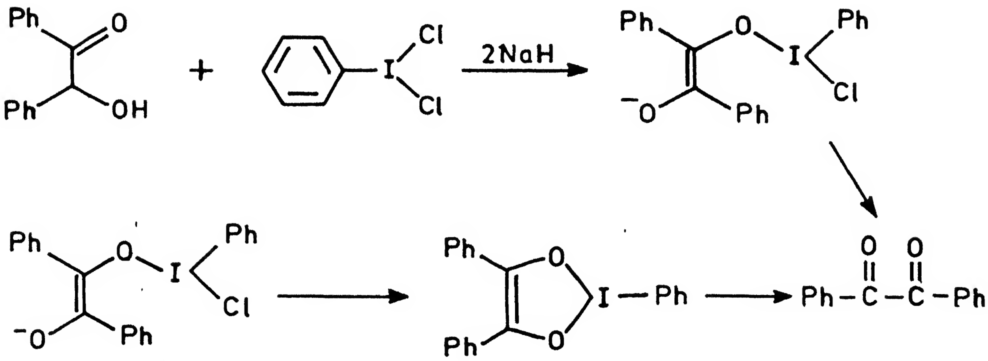
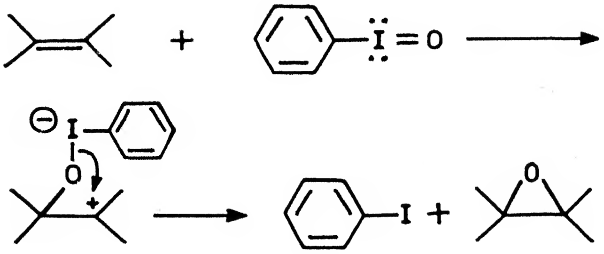


CHART B.5



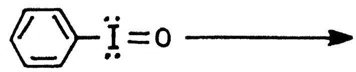
used.[19-21] The interaction of the π system with these reagents would perhaps facilitate the epoxidation. A wide range of compounds have been transformed to their oxides so that this reaction could be used with confidence for the preparation of epoxides (TABLE B.6). An interesting illustration is the reaction of iodosobenzene with cis- and trans-stilbenes in the presence of iron porphyrins. The cis stilbene formed selectively the cis -oxide whereas the trans stilbene was inert to this reagent.[22] In some cases, the initially formed epoxide could undergo rearrangement as illustrated with 2,4-di^{t}butyl cyclopentadienone.[26] In this case, the rearranged lactone is also obtained which is rationalized in CHART B.6.

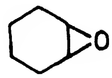
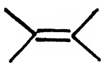
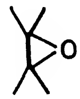
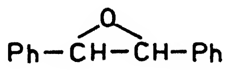
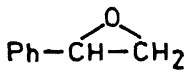
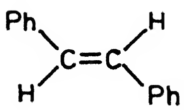
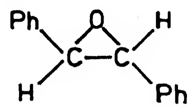
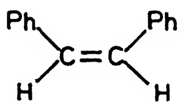
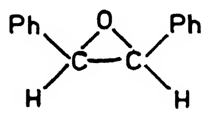
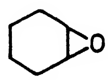
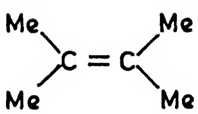
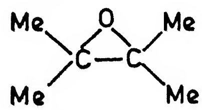
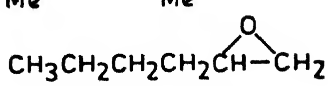
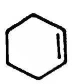
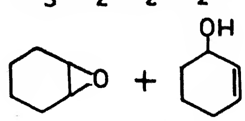
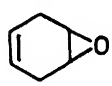
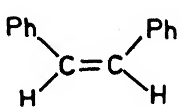
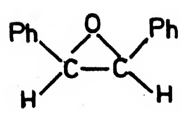
An interesting reaction of iodoso-benzene is the efficient formation of cyclic ethers from allyltrimethylsilyl systems that carry an ω-hydroxyl function at the 2 position of the allyl unit[27,28] (TABLE B.7). This reaction, which is quite useful, can be understood in terms of pathways indicated in CHART B.7.

Interesting variations of the cyclization has been realized via trimethyl germanes, as well as the utilization of carboxyl group leading to lactones.[28] An unusual reaction of iodosobenzene is its ability to bring about the transformation of a variety of ketenes to α-lactones (TABLE B.8). The reaction could be envisaged as taking place via the attachment of the iodosyl oxygen to the terminal carbon of the ketene functional

TABLE B.6

REACTION TYPE

X +  Z

X	Y	Z	Ref.
	Y, Fe-Perphyrins		19
	"		19
Ph-CH=CH-Ph	Y, $FeCl_3$		20
Ph-CH=CH_2	"		20
	Y, $Cu(NO_3)_2$		21
	"		21
	"		21
	"		21
$CH_3CH_2CH_2CH_2CH=CH_2$			21
	Y, Fe-Porphine Complexes.		22
	"		22
	"		22

CONTD.

TABLE B.6

REACTION TYPE (CONTD.)

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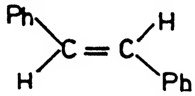
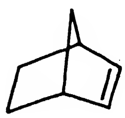
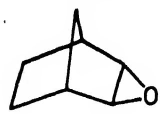
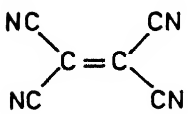
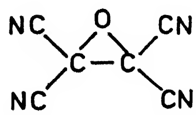
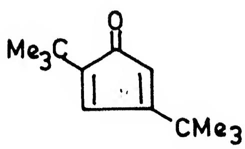
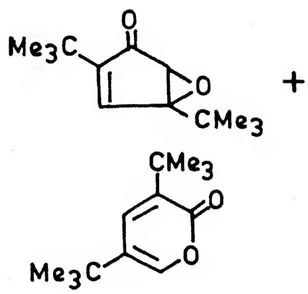
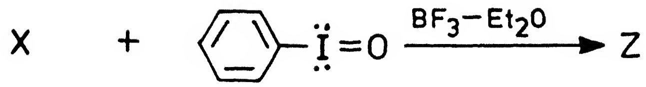
	Y, Fe−Porphine complexes	Inert [No Rexn.]	22
$Ph-CH=CH_2$	Y, Fe or Mn−Tetraaryl Porphyrins	$Ph-\overset{O}{\widehat{CH-CH_2}}$	23
$PhO-CH_2(CH_2)_3CH=CH_2$	"	$PhO-CH_2(CH_2)_3\overset{O}{\widehat{CH-CH_2}}$	23
$CH_3(CH_2)_3CH=CH_2$	"	$CH_3(CH_2)_3\overset{O}{\widehat{CH-CH_2}}$	23
$CH_3(CH_2)_3CH=CH_2$	"	$CH_3(CH_2)_2CH=CH-CH_2OH$	23
$CH_3(CH_2)_3CH=CH_2$	"	$CH_3(CH_2)_3CH_2CHO$	23
$CH_3(CH_2)_6CH=CH_2$	Y, Porphyrin Fe−complexes	$CH_3(CH_2)_6\overset{O}{\widehat{CH-CH_2}}$	20
	Y, Cr		24
	Y		25
	Y, TPPMn(III)Cl		26

TABLE B.7

REACTION TYPE



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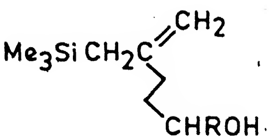
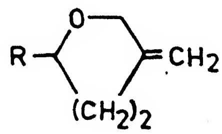
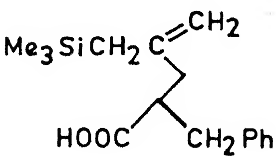
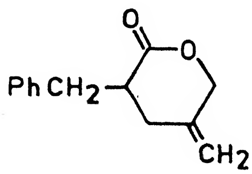
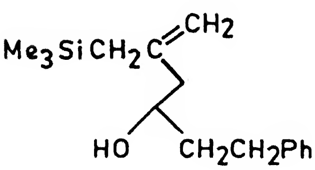
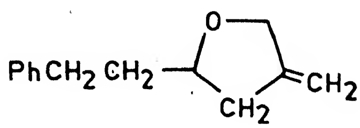
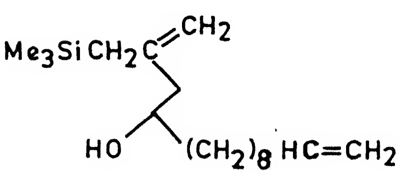
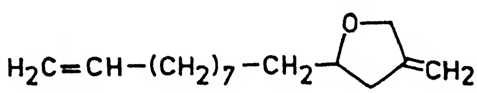
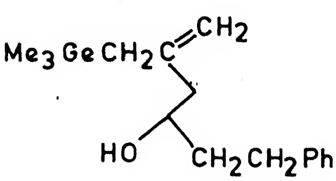
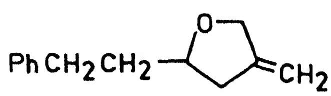
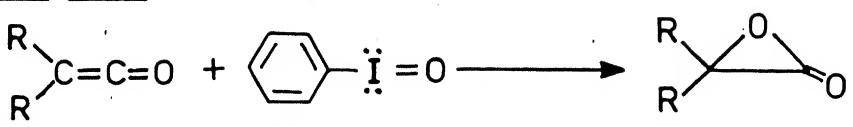
 R = hexyl, heptyl		27
		28
		28
		28
		28

TABLE B.8

REACTION TYPE



R	Ref.
$-CH_3$	25
$-C_2H_5$	25
$-CF_3$	25
$-Ph$	25

CHART B.6

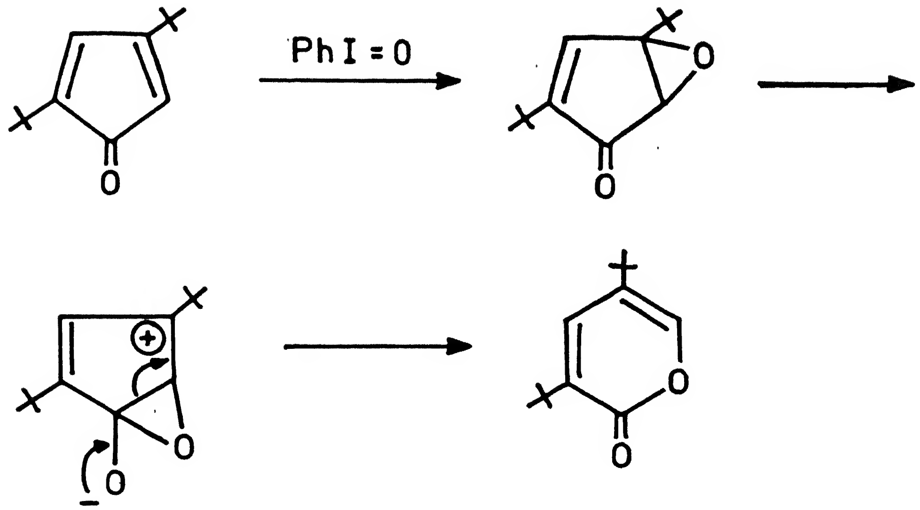


CHART B.7

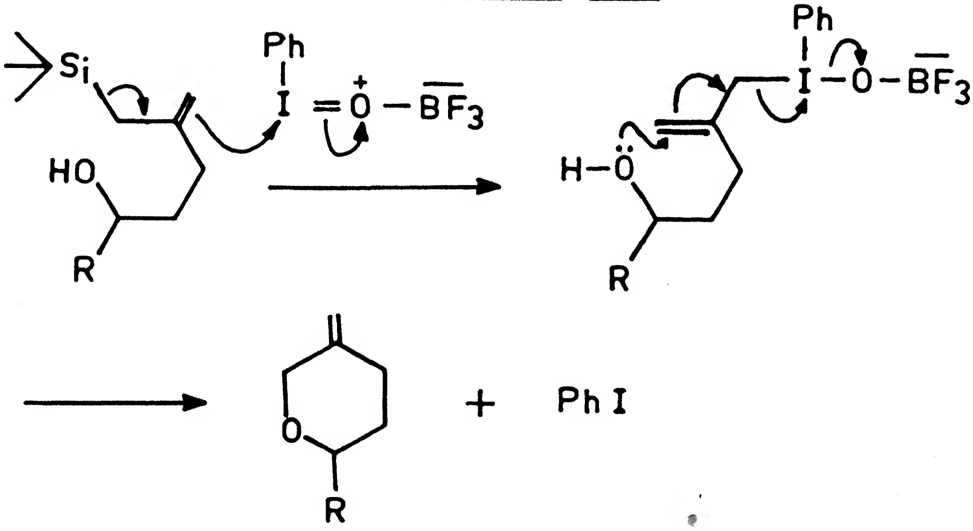
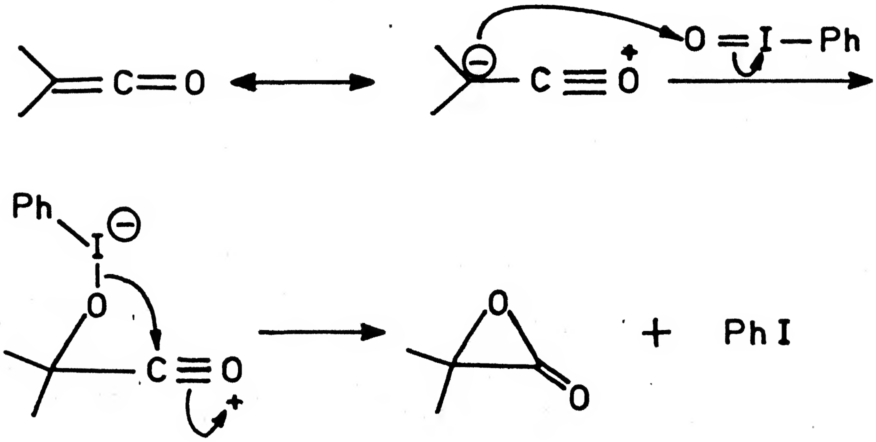


CHART B.8



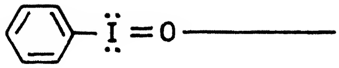
group,[25] which undoubtedly is facilitated by contribution from the ketene carbonyl as envisaged in CHART B.8. Thus, the mechanism is very close to that for the epoxidation of olefins. Phenols, secondary alcohols and primary alcohols are readily oxidized with iodosobenzene to the corresponding aldehydes.[29] The reaction is particularly useful in the transformation of either 1,2- or 1,4-dihydroxy aromatic systems to the corresponding quinones (TABLE B.9).[30,31] The transformation to the carbonyl compounds is envisaged as presented in CHART B.9.

The aldehydes, in turn, are transformed to carboxylic acids in the presence of ruthenium triphenylphosphine complexes[29,32] (TABLE B.10). This transformation is rationalized in CHART B.10. An interesting fragmentation of the cyclohexyl system takes place <u>via</u> tertiary hydroxyl and facilated by an appropriately substituted tri-n-butyl tin functional group[68] (CHART B.11).

A variety of acetylenic groupings are transformed to the 1,2-diketones with iodoxybenzene (TABLE B.11).[33,34] This reaction can be readily understood in terms of the mechanistic squences presented in CHART B.12, which finds much support that even enamines and enol ethers, readily undergo this transformation (CHART B.12). An expected but reliable transformation is the formation of sulphoxides from sulfides with iodosyl benzene.[32,35] It appears that in every case the oxidation stops at the sulphoxide stage (TABLE B.12). A very useful

TABLE B.9

REACTION TYPE

X +  Z

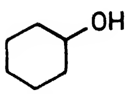
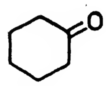
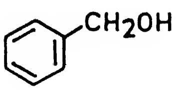
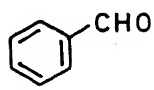
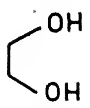
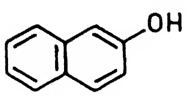
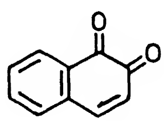
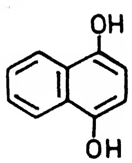
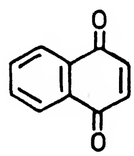
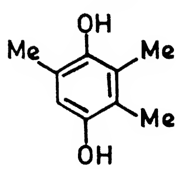
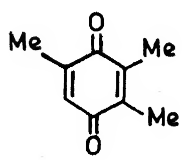
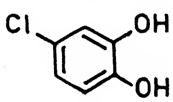
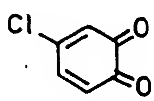
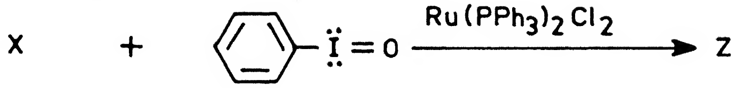
X	Y	Z	Ref.
RCH_2OH R = aromatic, aliphatic, alicyclic, terpenoid	Y, $Ru(PPh_3)_3Cl_2$	RCHO	29
$CH_3(CH_2)_7OH$	,,	$CH_3(CH_2)_6CHO$ + $CH_3(CH_2)_6COOH$	29
	,,		29
Alcohals	Y, Chlorotetra-phenylporphinato Cr III	Aldehydes, or Ketons	24
	Y, Cr / Fe		30
	,,	OHC — CHO	30
			30
	Y		31
	,,		31
	,,		31

TABLE B.10

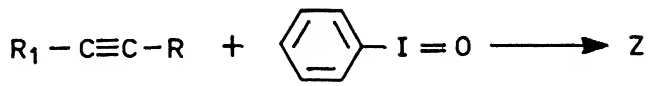
REACTION TYPE



X	Z	Ref.
RCHO	RCOOH	29
$CH_3(CH_2)_6CHO$	$CH_3(CH_2)_6COOH$	29
RCH_2OH	RCHO + RCOOH	32

TABLE B.11

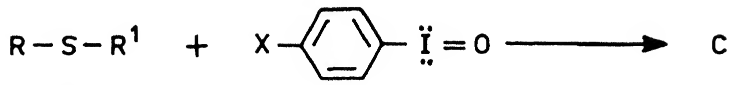
REACTION TYPE



X	Y	Z	Ref.
$R = OEt$, $R_1 = Ph$	Y, $RuCl_2(PPh_3)_3$	$Ph-C(=O)-C(=O)-OEt$	33
$R = NEt_2$, $R_1 = Ph$	"	$Ph-C(=O)-C(=O)-N(Et)_2$	33
$R = R_1 = Ph$	"	$Ph-C(=O)-C(=O)-Ph$	34
$R = C_5H_{11}$, $R_1 = Ph$	"	$Ph-C(=O)-C(=O)-C_5H_{11}$	34
$R = Me$, $R_1 = Ph$	"	$Ph-C(=O)-C(=O)-Me$	34
$R = Et$, $R_1 = Me$	"	$Me-C(=O)-C(=O)-Et$	34
$R = OR_2$	Y, Ru	$R_1-C(=O)-C(=O)-OR_2$	34
$R = N(R_2)_2$	"	$R_1-C(=O)-C(=O)-N(R_2)_2$	33

TABLE B.12

REACTION TYPE



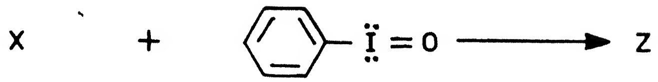
A B

A	B	C	Ref.
$R-S-R^1$	$X = NO_2$, $RuCl_2(PPh_3)_2$	$R-\overset{+}{S}(O^-)-R^1$	32
$R-S-R^1$	$X = OMe$, $RuCl_2(PPh_3)_2$	$R-SO_2-R^1$	32
$R = R^1$	X = H, Metallo-Porphyrin chloride	$R-\overset{+}{S}(O^-)-R$	35
$R = R^1 = CH_2Ph$	,,	$PhCH_2-\overset{+}{S}(O^-)-CH_2Ph$	35
$R = R^1 = Bu$	,,	$Bu-\overset{+}{S}(O^-)-Bu$	35
$R = R^1 = C_2H_5$	,,	$H_5C_2-\overset{+}{S}(O^-)-C_2H_5$	35
$R = R^1 = CMe_3$	,,	$Me_3C-\overset{+}{S}(O^-)-CMe_3$	35
$R = R^1 = Ph$	,,	$Ph-\overset{+}{S}(O^-)-Ph$	35

CONTD.

TABLE B.12

REACTION TYPE (CONTD.)



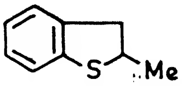
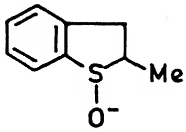
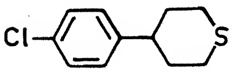
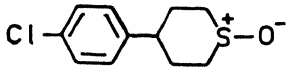
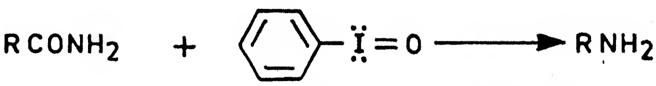
X	Y	Z	Ref.
	Y, Metallo-Porphyrin chloride		35
			35
$R-S-R_1$	Y, Cr	$R-\overset{+}{S}(O^-)-R_1$	30

TABLE B.13

REACTION TYPE



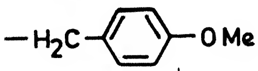
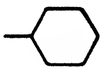
R	Ref.
—Pentyl	36
$-CH_2CHMe_2$	36
$-CMe_3$	36
$-CH_2CH_2Ph$	36
$-CH_2Ph$	36
	36
	36

CHART B.9

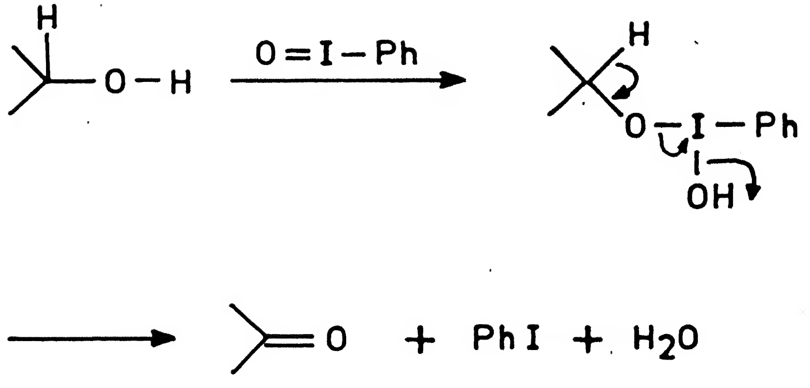


CHART B.10

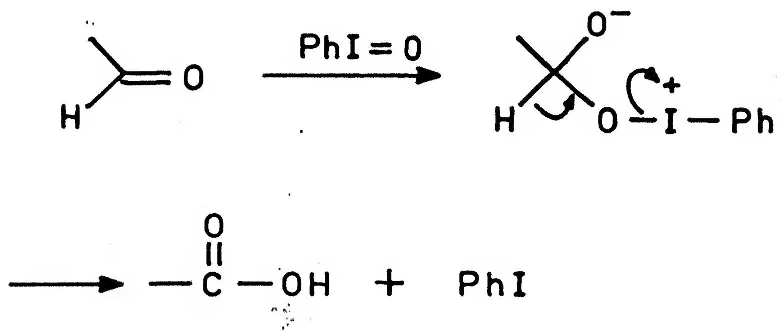
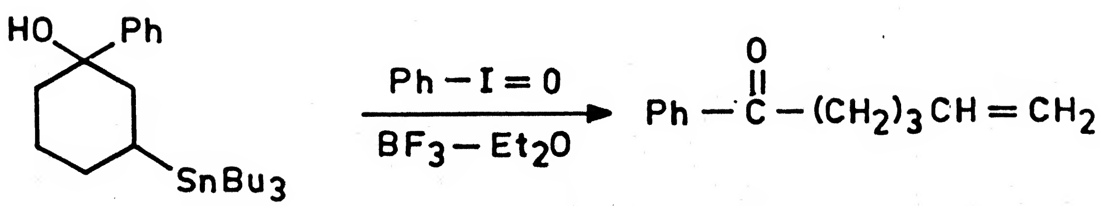


CHART B.11



reaction that has already found wide applicability is the ability of iodoxybenzene to bring about the degradation of primary amides to primary amines.[36] The experimental complexities associated with the usual Hoffmann degradation with hypobromite can be very easily overcome with this reagent. The reaction is usually done in the presence of pyridine and trifluoroacetic acid. The overall process, rationalized in CHART B.13 envisages the prior nucleophilic addition to the iodosyl benzene forming the nitrogen-iodine bond. The alternate possibility, namely, the attack of the nitrogen at the oxygen end of iodoxy benzene is unlikely, particularly because even diacetoxy or ditrifluoroacetoxy iodobenzenes also undergo this reaction (vide infra) (TABLE B.13, CHART B.13).

A related, but extremely unusual reaction, is the transformation of heterocyclic systems of the type presented in CHART B.14 with iodosylbenzene in which the aromatic moiety as well as iodine, are incorporated in the substrate.[37] This extraordinary reaction is envisaged as taking place via initial acceptance of iodoxybenzene, formation of the conjugate base, fragmentation involving the rupture of the phenyl iodine bond with concomittant phenyl transfer to the oxygen (CHART B.14). Terminal acetylenes can be transformed to the corresponding carboxylic acids with loss of carbon using iodosobenzene in the presence of triphenylphosphine ruthenium dichloride.[34] It may be recalled that these conditions were used for the trans-

CHART B.12

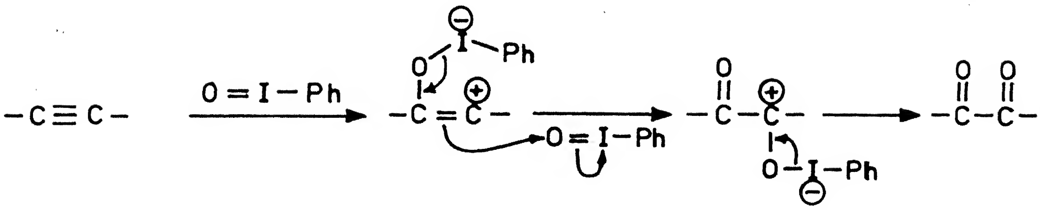


CHART B.13

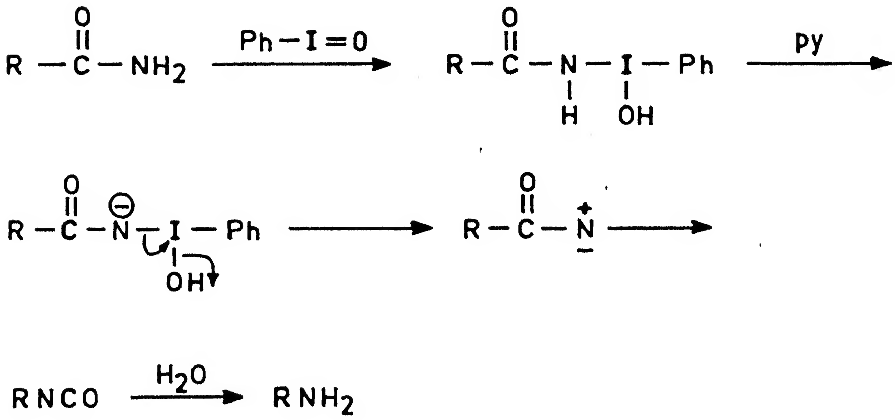
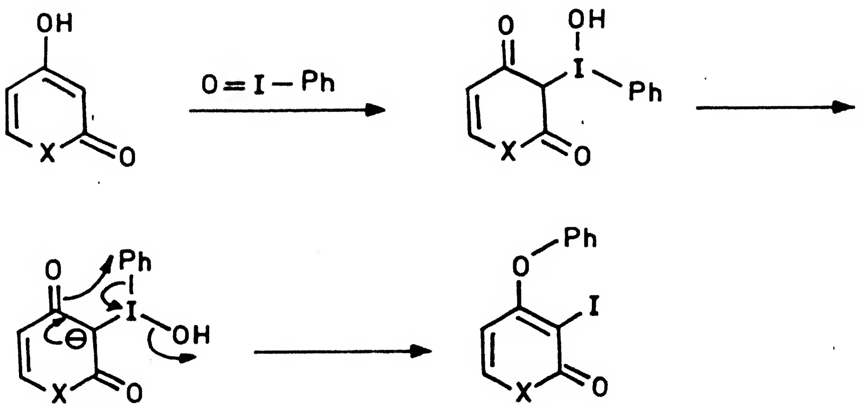


CHART B.14



formation of disubstituted acetylenes to 1,2-dicarbonyl compounds. Consequently, the overall change can be understood in terms of formation of an α-keto aldehyde which is further oxidised to the carboxylic acid with loss of a carbon (TABLE B.15). Finally, some other transformations brought about by iodosobenzene are summarized in TABLE B.16.

III. Reactions of Phenyl Iodosoacetates

Both $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$ have became very important reagents in the sense that they are widely used for the transformation of amide functions to amines.

The pathway by which this transformation takes place is presented in CHART B.15.

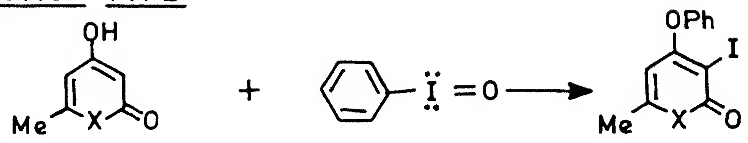
A reliable transformation mediated by phenyl iodosoacetate is the transformation of a variety of amines to the corresponding azo compounds[39] (TABLE B.17). The formation of benzofuran oxides from o-nitroanilines[40] can best be explained on the basis of nitrene intermediates.

IV. Reactions of Iodoxybenzene

Till our investigations relating to iodoxybenzene and related compounds as possible ozone equivalents, the application of this reagent was largely confined to oxidation of aromatic hydroxyl groupings as illustrated in TABLE B.18.

TABLE B.14

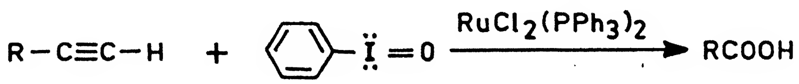
REACTION TYPE



X	Ref.
$-O-$	37
$-NH-$	37
$-NPh-$	37

TABLE B.15

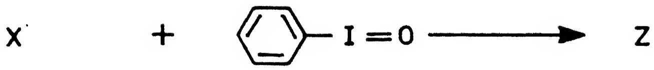
REACTION TYPE



R	Ref.
$-Ph$	34
$-C_6H_{13}$	34
$-C_5H_{11}$	34

TABLE B.16

REACTION TYPE



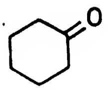
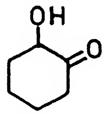
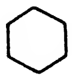
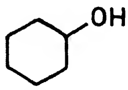
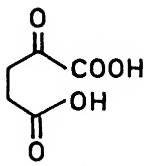
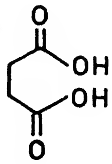
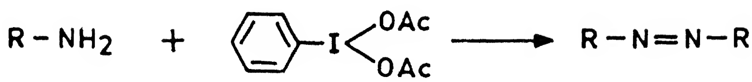
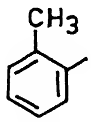
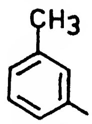
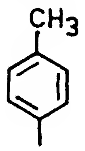
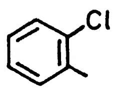
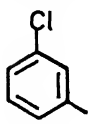
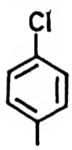
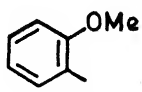
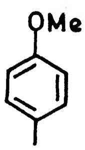
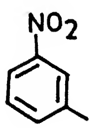
X	Y	Z	Ref.
	Y		25
$RCH=C=O$	Y	$R-\overset{O}{\overset{\Vert}{C}}-COOH$	25
$R-CH_3$	Y, Fe-Porphine Complexes	RCH_2OH	22
	,,		22
Hydrocarbons	Y, Chlorotetra-Phenylporphinato Cr III	Epoxides + Alcohols	24
Camphor	Y, Cytochrome P450	5-exo-hydroxylation of camphor	38
	Y		25

TABLE B.17

REACTION TYPE

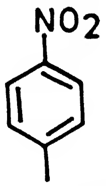
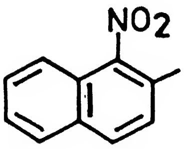
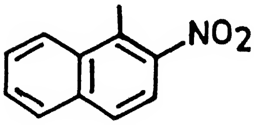


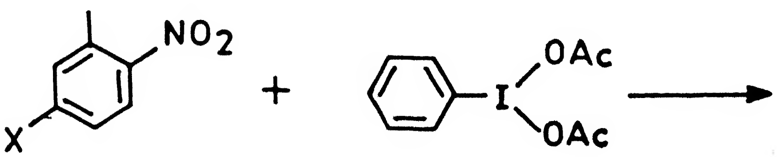
R	Ref.
−Ph	39
	39
	39
	39
	39
	39
	39
	39
	39
	39

CONTD. ____

TABLE B.17

REACTION TYPE (CONTD.)

R	Ref.
	39
	40
	40

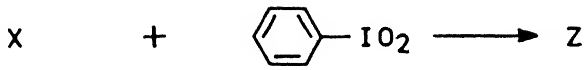


Benzofuran Oxides 40

X = Me, Cl, OMe

TABLE B.18

REACTION TYPE



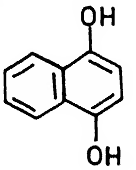
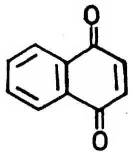
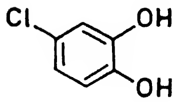
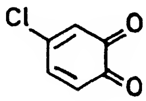
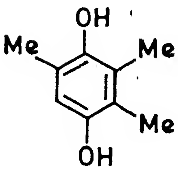
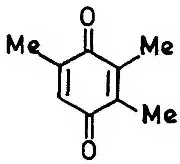
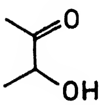
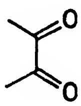
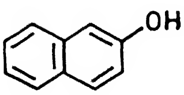
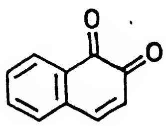
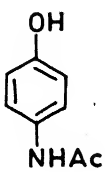
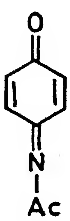
X	Z	Ref.
		31
		31
		31
		41
		41
		42

CHART B.15

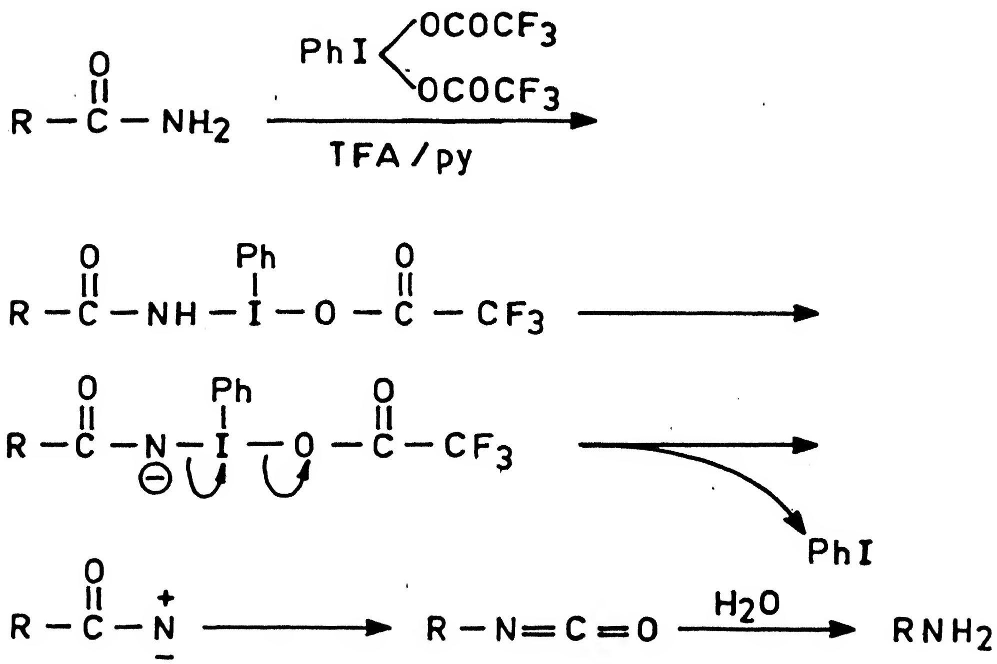
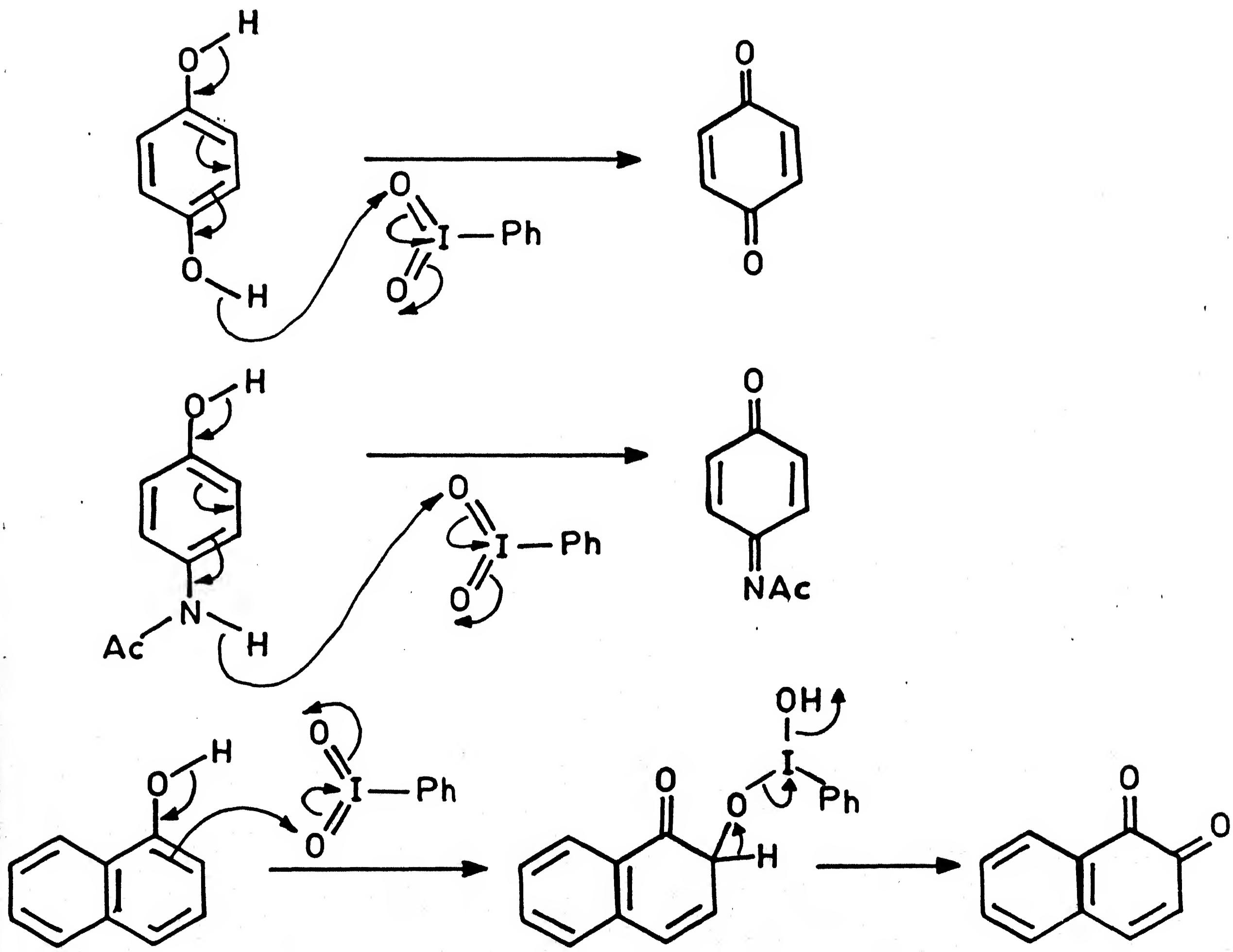


CHART B.16

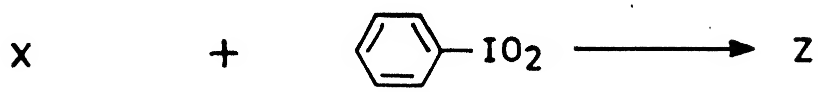


The transformation of aromatic dihydroxy compounds to quinones[31] and similar oxidations of related systems can be best understood on the basis of phenyl iodoxybenzene as a hydride acceptor (CHART B.16). The formation of naphthaquinone from α-naphthol[41] can also be understood in terms of initial oxidation followed by decomposition of the intermediate, leading to product and iodobenzene (CHART B.16). In addition to these, there were examples where iodoxybenzene was demonstrated to oxidise sulfides.

Recent work from these laboratories have shown that iodoxybenzene could behave in a manner that resembles ozone. Thus, diphenylacetylene gives benzil and 1,1,4,4-tetraphenyl-1,3-butadiene leads to the formation of benzophenone[41] (TABLE B.19). It is also shown that the condensed aromatic systems phenanthrene, acenaphthalene and pyrenes lead to formation of quinones in attractive yields[41] (TABLE B.20). Like ozone, iodoxybenzene reacts with aralkyl groupings leading to ketonic products arising from insertion to the active C-H bond. This aspect has been illustrated in TABLE B.21. Present work confirm our findings related to the ability of iodoxybenzene to cleave π systems to carbonyl compounds. Another unexploited transformation of iodoxybenzene is the ready transformation of this reagent to iodosodiacetate and iodotetraacetates on treatment with various acid anhydrides.[43,44] It is possible that these compounds would have properties that are parallel to the

TABLE B.19

REACTION TYPE



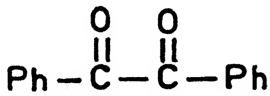
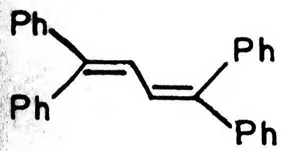
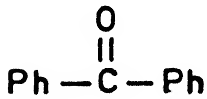
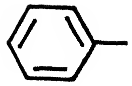
X	Z	Ref.
$Ph-C\equiv C-Ph$		41
		41

TABLE B.20

REACTION TYPE

X +  $-IO_2$ ⟶ Z

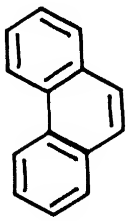
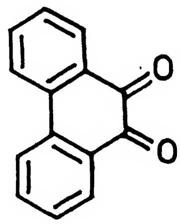
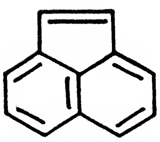
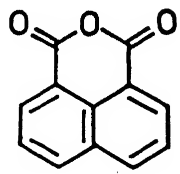
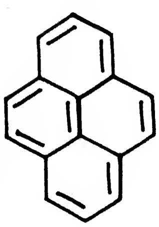
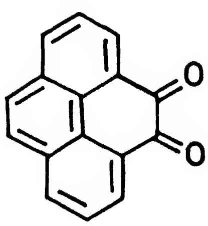
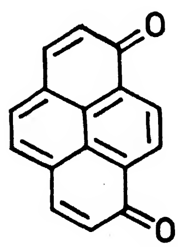
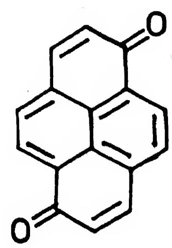
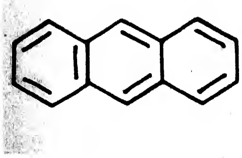
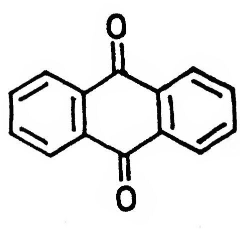
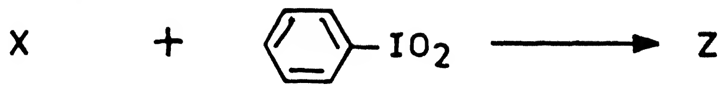
X	Z	Ref.
		41
		41
	 +  + 	41
		41

TABLE B.21

REACTION TYPE



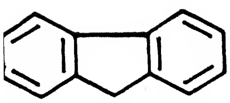
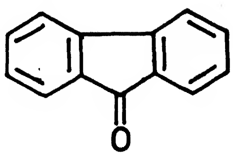
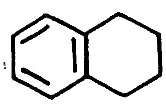
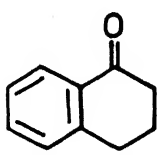
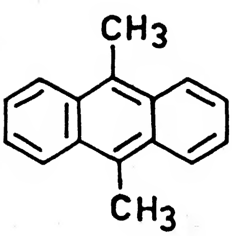
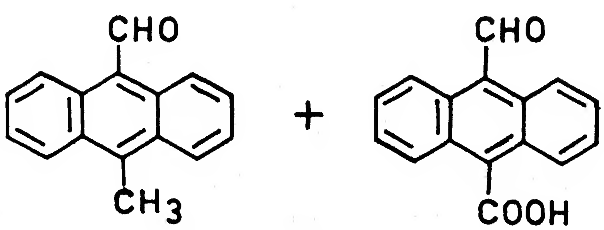
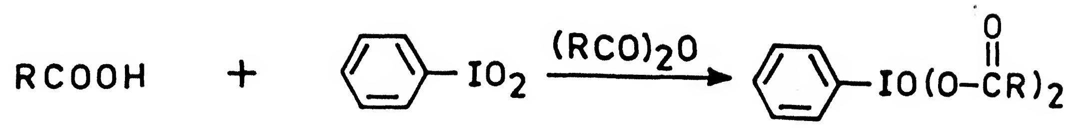
X	Z	Ref.
RCH_2Ph	$R-\overset{O}{\overset{\Vert}{C}}-Ph$	41
$PhCH_2Ph$	$Ph-\overset{O}{\overset{\Vert}{C}}-Ph$	41
		41
		41
		41

TABLE B.22

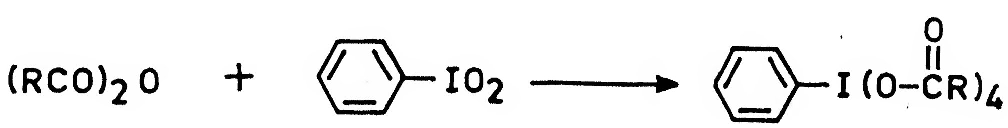
REACTION TYPE



R	Ref.
$-CH_3$	43
$-CF_3$	43
$-C_3H_7$	43

TABLE B.23

REACTION TYPE



R	Ref.
$-CF_3$	44
$-C_3F_7$	44

iodosobenzene acetates (TABLE B.22).

The following section outlining the present work concerns itself with the investigation of the potential of iodoxybenzene. A major draw back relating to the use of iodoxybenzene is its very high insolubility in practically all solvents, thus limiting its utility in chemical transformations. This problem has been overcome to some extent by attaching a hydrophobic residue, making it readily soluble in chlorobenzene and nitrobenzene.

The hypervalent iodine compounds would continue to attract investigation, because of their potential in transfer reactions. The brief account that has been presented in this section would hopefully illustrate this point.

C. PRESENT WORK

The genesis of the present work arises from an analysis of reactions which, whilst allowed by the Woodward-Hoffmann rules, do not take place. While these rules predict the allowedness or otherwise of a particular reaction, they do not specify whether kinetic or thermodynamic barriers would permit the occurrence of such a reaction. An analysis of a large variety of such reactions carried out in the present laboratory, some time ago, led to interest in the nitro group as a possible ozone equivalent. In complete contrast to the high reactivity of ozone to π systems, the isoelectronic nitro group is inert to these functions. Various considerations have led to the conclusion that the exceptionally high heat of formation of ozone (+34 kcal mol^{-1}) is a major reason for its reactivity. This analysis also showed that the modest unfavourable activation energy associated with a hypothetical addition of nitrobenzene to π systems could be overcome by perturbation of this molecule with electron withdrawing substituents. A modest amount of success was obtained in the study of variously perturbed nitrobenzenes as possible ozone equivalents. However, solubility and reactivity considerations set a limit towards the use of perturbed nitro-aromatics as ozone equivalents and suggested that an equivalent, but entirely

different system, which could have enhanced reactivity should be explored. This led to the logical identification of iodoxybenzene. Iodoxybenzene, possessing a functional group that is isoelectronic to ozone and the nitro group, can be expected to have a substantially positive heat of formation and additionally, the highly polarized I-O bond in this compound can be anticipated to reduce the kinetic activation energy barrier. In the event, iodoxybenzene turned out to be a reagent of promise and exhibited properties remarkably parallel to that of ozone.[41] A severe drawback of iodoxybenzene utility was that it was practically insoluble in most solvents, thus preventing its wide use in chemical reactions. It was felt that this serious impediment could be overcome by attachment of hydrophobic residues to the aromatic moiety. Such investigations have led to the synthesis of 4-^{t}butyl iodoxybenzene and its demonstration as a practical and reliable ozone equivalent. The thrust of the present work is then to assess the utility of this reagent so that it could be used with confidence in organic synthetic operations.

The preparation of title reagent, 4-^{t}-Butyl iodoxybenzene (1), is outlined in CHART C.1. The reaction of benzene with t-butyl chloride under Friedel Craft's conditions gave 46% of t-butyl benzene which on reaction with iodic acid in the presence of iodine in aqueous medium at reflux gave 4-^{t}butyl iodobenzene (2) in more than 70% yields. Compound (2), in turn,

on treatment with dry chlorine under ice-salt conditions, gave, the novel 4-^{t}butyl iodobenzene dichloride (3), mp 84^{o} which was found as a stable compound and soluble in solvents such as chloroform and benzene. The utility of 4-^{t}butyl iodobenzene dichloride (<u>3</u>) as a reagent has also been investigated in the present work (<u>vide</u> <u>infra</u>). The reactions of 4-^{t}butyl iodobenzene dichloride (<u>3</u>) with NaOCl in acetic acid under very carefully controlled conditions gave 4-^{t}butyl iodoxybenzene in 85% yield. 4-^{t}Butyl iodoxybenzene (<u>1</u>) is a stable and crystalline compound, mp 217-221^{o} which on melting, demonstrated violent decomposition. However, during numerous oxidations with (<u>1</u>), no explosion or mishaps occurred. The estimated solubility of (<u>1</u>) in hot benzene, chlorobenzene and nitrobenzene are respectively 0.2%, 6% and 9%. These values should be compared to the practical insolubility of the parent iodoxybenzene in these solvents.

<u>1</u>: mp : 217-221^{o}C (explodes!)

ir : ν_{max} (KBr) cm^{-1}: 1620, 1490, 1470, 825, 550.

<u>2</u>: bp : 114^{o}C/0.05 torr.

ir : ν_{max} (neat) cm^{-1}: 1500, 1400, 1370, 1270, 820, 720.

nmr : δ (CCl_4), 60 MHz: 1.3 (s, 9 H, tert-butyl), 7.03 (d, J = 8 Hz, 2 H, aromatic), 7.52 (d, J = 8 Hz, 2 H, aromatic).

CHART C.1

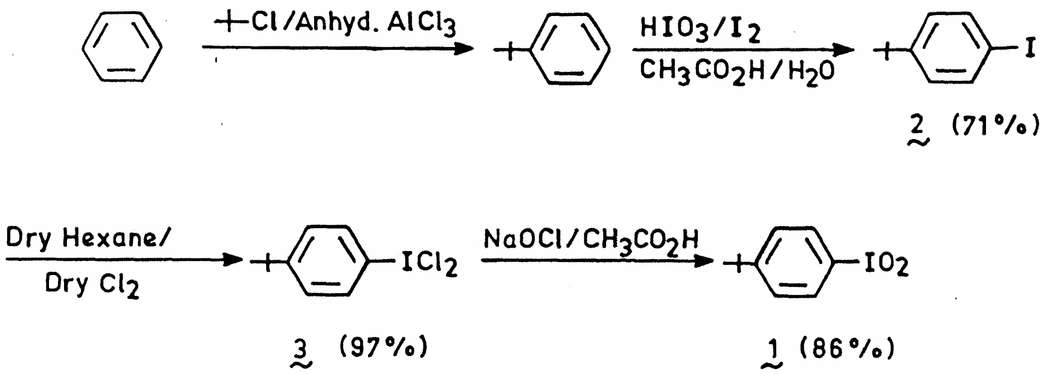
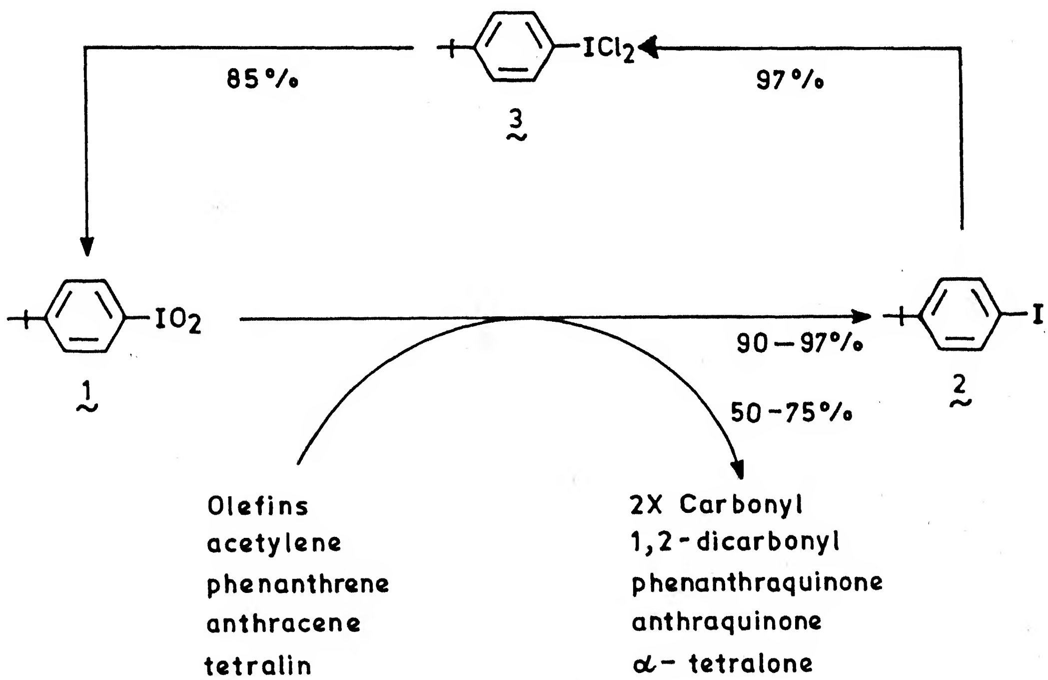


CHART C.2



3: mp : $84^{\circ}C$.

ir : ν_{max} (KBr) cm^{-1}: 1510, 1410, 1280, 830, 560.

nmr : δ ($CDCl_3$), 60 MHz: 1.36 (s, 9 H, tert-butyl), 7.46 (d, J = 8 Hz, 2 H, aromatic), 8.06 (d, J = 8 Hz, 2 H, aromatic).

4-^{t}Butyl iodoxybenzene (1) was found to be an excellent oxygen transfer reagent in the sense that the reaction of (1) with various substrates led to nearly total recovery of 4-^{t}butyl-iodobenzene (2) which could be recycled. This aspect and the general profile of this reagent is presented in CHART C.2. Thus, the transformations brought about with 4-^{t}butyl iodoxy-benzene, are clean, the products directly isolable and the resulting (2) effectively recycled.

Type I: Reactions of 4-^{t}Butyl Iodoxybenzene

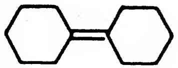
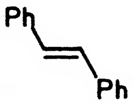
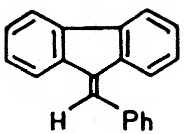
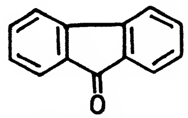
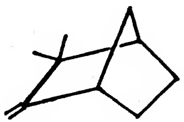
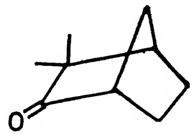
The transformation brought about under this category have a profile very similar to that of ozone as illustrated in CHART C.3. In this, the π system is cleaved to the dicar-bonyl compounds, a process that is envisaged as taking place by a $\pi^4s + \pi^2s$ route with the resulting direct cleavage of the adduct to (2) and the carbonyl function. The similarity of this reaction pathway with that of ozone is upto the first cycloaddition stage. In the case of ozone the primary ozonide

undergoes fragmentation and a second cycloaddition to the secondary ozonide which has to be reduced to the dicarbonyl system (CHART C.3).

The π bond cleavage as envisaged in CHART C.3, can be carried out either in hot chlorobenzene or nitrobenzene. The former solvent is preferred and at a temperature of about 130-140°C. The workup is very simple, involving the evaporation of chlorobenzene in vacuo and chromatography over silica gel. The 4-^{t}butyl iodobenzene (2) can be recovered in nearly quantitative yields on elution with hexane and all the products with the benzene-hexane mixture. The type I profile of 4-^{t}butyl iodoxybenzene is illustrated in the present work with substrates shown in TABLE C.1. As could be seen from this table a variety of olefins including aliphatic, aromatic, fully substituted, trisubstituted and disubstituted π systems do undergo this reaction, leading to the formation of the expected products in good yields (TABLE C.1).

TABLE C.1 presents the substrates that were employed to illustrate the potential of 4-^{t}butyl iodoxybenzene (1), as an ozone equivalent. The table also provides details relating to the reaction conditions, the solvent employed, the relative proportions of the reagent used, pure isolated yields of the ketones, and the amount of 4-^{t}butyl iodobenzene (2) recovered which was recycled. The biscyclohexylidene used was conveniently prepared by the procedure of Barton and Willis and

TABLE C.1

SUBSTRATE (m mol)	IO_2 (m mol)	SOLVENT (ml)	TIME(h)	PRODUCT (% Yield)	I (% Yield)
 (2)	2.5	PhCl (10)	2	 (59)	91
 (1)	2.0	PhCl (8)	6	PhCHO (67) PhCOCOPh (20)	94
 (0.5)	0.5	PhCl (8)	7	 (50) PhCHO (45)	92
Ph−C≡C−Ph (0.5)	1.0	PhCl (8)	18	PhCOCOPh (66)	91
(1.0)	1.5	$PhNO_2$ (2)	10	PhCOCOPh (57)	—
 (1.0)	1.0	PhCl (5)	10	 (48)	—
(0.5)	1.0	$PhNO_2$ (5)	8	(63)	—

as shown in CHART C.4.

Type II: Reactions of 4-^{t}Butyl Iodoxybenzene

From TABLE C.1 it could be seen that in the reaction of trans stilbene with the reagent (1), in addition to benzaldehyde (67%), there was also isolated benzil (20%). In this reaction, the π system is converted into a 1,2-dicarbonyl unit. This is a feature of iodoxybenzene and 4-^{t}butyl iodoxybenzene, namely π systems which are endowed with vicinal hydrogens are transformed to 1,2-diketones. The pathway associated with this type of transformation, is illustrated in CHART C.5. Comparison of CHART C.3 and CHART C.5 would show that the primary reaction in both cases is a cycloaddition. However, the presence of the aryl hydrogens in the adduct enables fragmentation leading to a ketal unit which then undergoes further oxidation to the observed 1,2-diketone. Naturally, this pathway is not commonly encountered in the reactions of ozone. This must be as a resultant greater propensity for the primary ozonide to fragment, leading to a carbonyl group and a zwitterionic species, rather than to undergo fragmentation as envisaged in CHAPRT C.5. Interestingly enough, wherever a driving force is afforded for the fragmentation of the initially formed ozonide along the lines illustrated in CHART C.5, such a change does indeed take place. Of particular significance is the observation that in sharp contrast to its mode of action on phenanthrene, ozone

CHART C.3

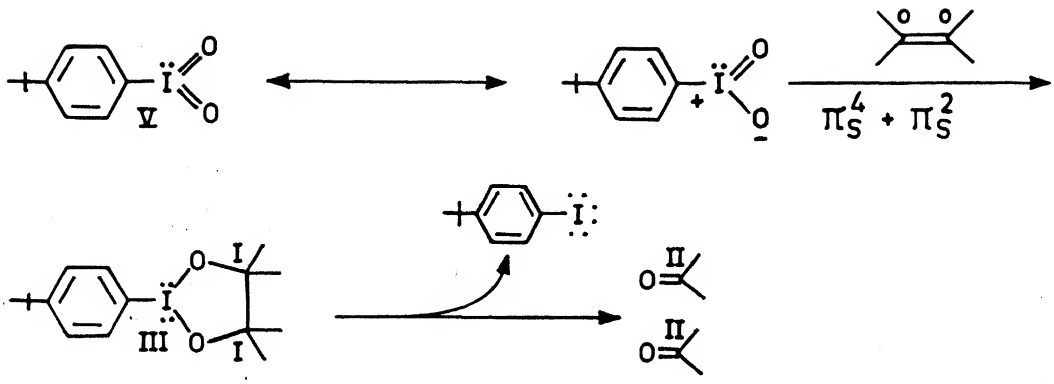


CHART C.4

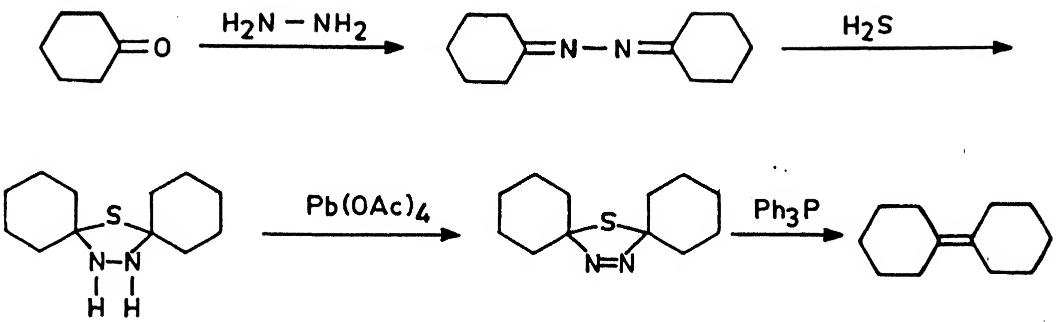
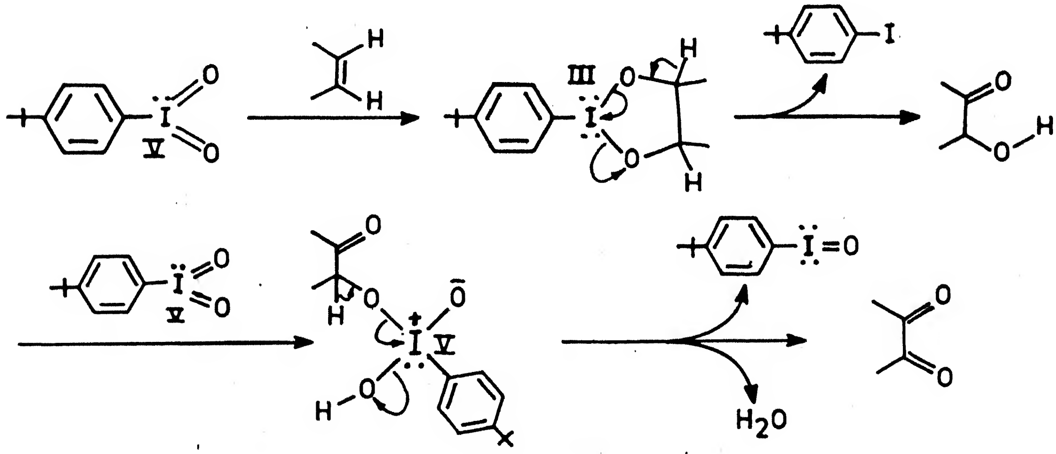


CHART C.5



transforms phenanthrene-9 carboxylic acid to phenanthrenequinone in 67% yields by pathways that closely parallel the phenanthrene ⟶ phenanthrenequinone change, mediated by (1). This must be attributed to the promotion of C-O bond fission by the carboxylic function in preference to the C-C fission, normally encountered with primary ozonides. An excellent illustration of the Type II reaction of 4-^{t}butyl iodoxybenzene which is expected to have good practical utility is the transformation of phenanthrene to phenanthrenequinone with two equivalents of the reagent in chlorobenzene at 140^o for 10 h leading to an excellent yield of phenanthrenequinone (75%) and nearly total recovery of 4-^{t}butyl iodobenzene (97%), which could be recycled. This transformation represents the most attractive amongs the several pathways available for oxidation of phenanthrene to phenanthrenequinone (CHART C.6).

Type III: Reactions of 4-^{t}Butyl Iodoxybenzene

In this mode, the peripositions of condensed aromatic systems are transformed to diketones with 4-^{t}butyl ioxoxybenzene. This type of reaction, which requires to equivalents of the reagent, is illustrated in CHART C.7 with the transformation of anthracene to anthraquinone in 59% yield (CHART C.7). However, it is possible that the initially formed 4-^{t}butyl iodosobenzene (CHART C.7), could also play a role in further oxidations which would reduce the amount of the reagent (1)

needed to bring about such a change. Type III oxidations generally proceed by reaction of either iodoxybenzene[41] or 4-^{t}butyl iodoxybenzene, by attack on condensed aromatic systems at sites having the lowest atom localization energy.

<u>Type IV: Reactions of 4-^{t}Butyl Iodoxybenzene</u>

In this type of oxidation, 4-^{t}butyl iodoxybenzene exhibits properties similar to that of ozone, namely, the ability to insert to an aralkyl C-H bond as shown in CHART C.8. An excellent illustration of this type is the transformation of tetralin to α-tetralone in 60% yields upon reaction in chlorobenzene for 6 h (CHART C.9). In our opinion, this represents the best route for α-tetralone from tetralin. In this case also, 97% of 4-^{t}butyl iodobenzene was recovered.

<u>Type V: Reactions of 4-^{t}Butyl Iodoxybenzene</u>

To this category, belongs the reaction of (<u>1</u>) with aromatic amines leading to azo compounds in good yields. Thus, iodoxybenzene (<u>1</u>) exhibits properties similar to that of iodosobenzene and phenyl iododiacetate (Section B).[39] Although the mechanism of this transformation awaits experimental study, it is envisaged as taking place by either of the two possibilities shown in CHART C.10. Alternately, the overall transformation could, in principle, take place <u>via</u> aromatic nitroso compounds. Typical possibilities of the Type V change with reagent (<u>1</u>) is

CHART C.6

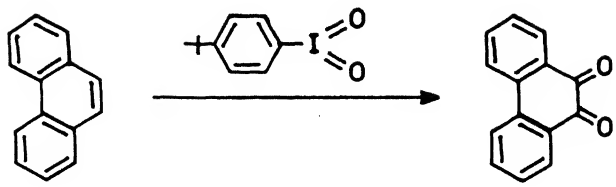


CHART C.7

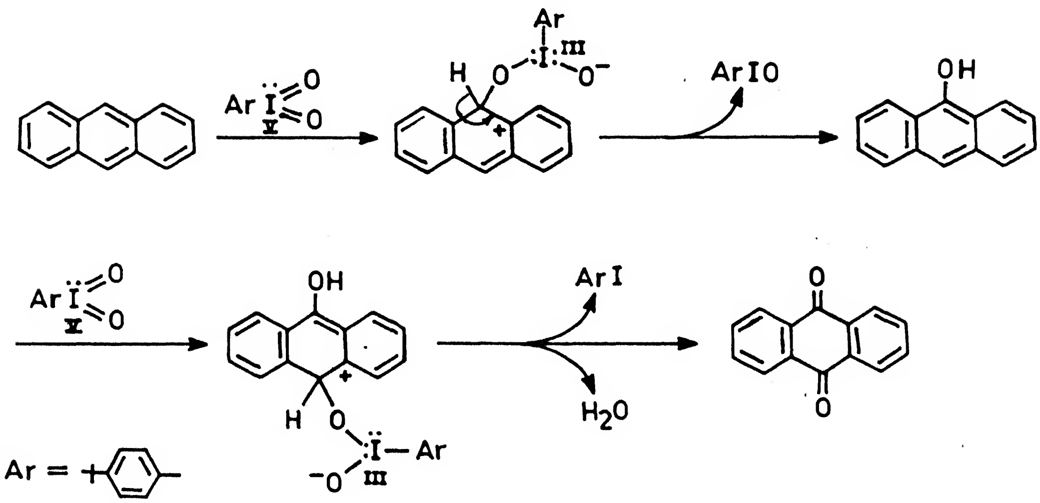


CHART C.8

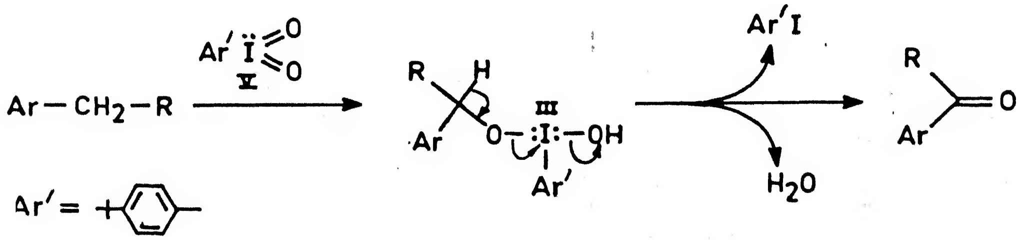


CHART C.9

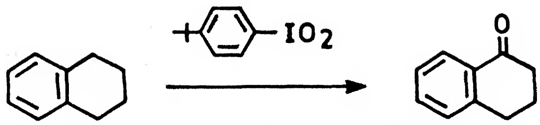


CHART C.10

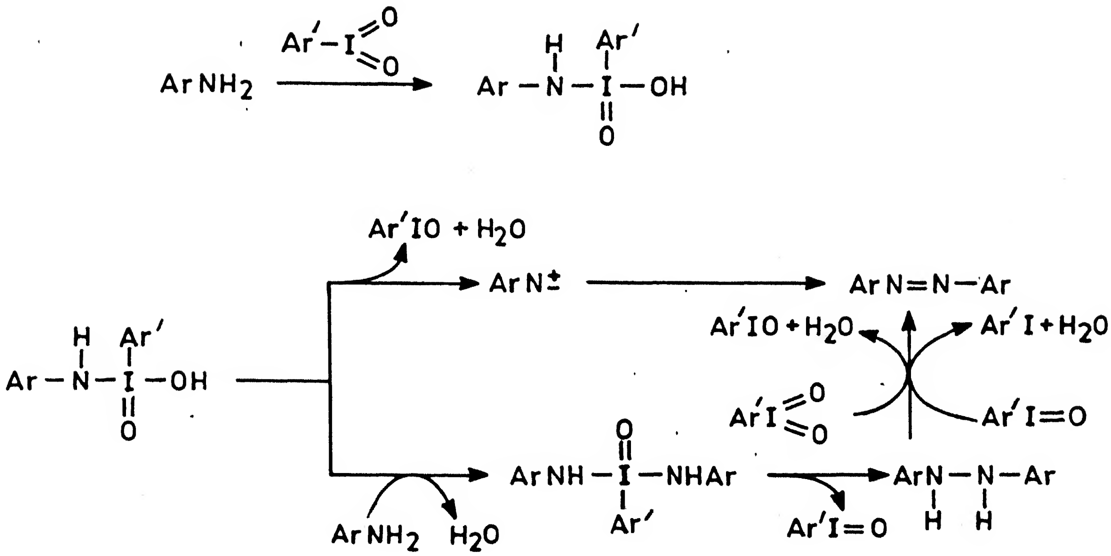
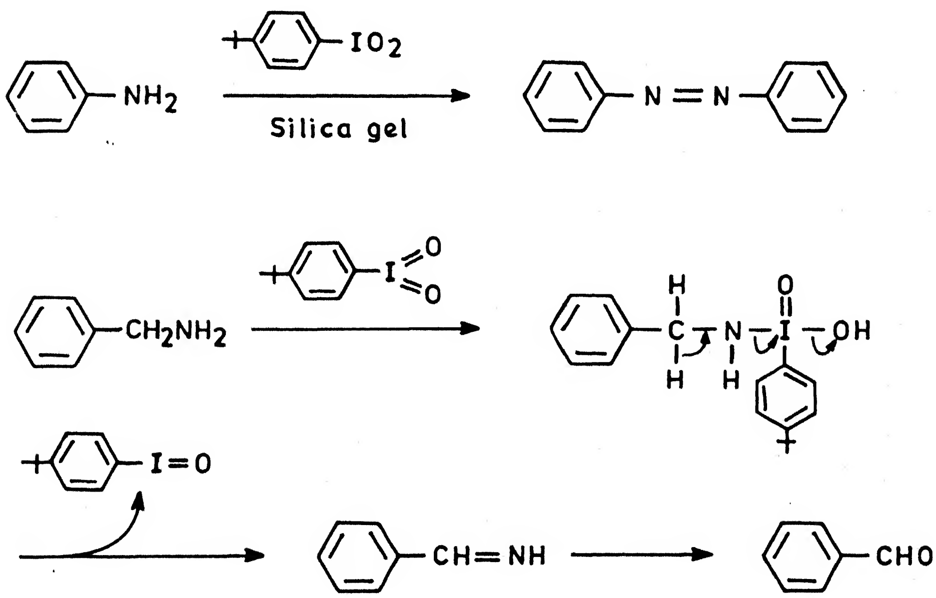


CHART C.11



illustrated in CHART C.11 with aniline and benzyl amine. In the case of the former, the product is azobenzene, isolated in over 60% yields; in the case of the latter, the product is benzaldehyde, obtained in about the same yield, which can readily be understood on the basis of fragmentation of the initially formed adduct, taking advantage of the proximate C-H bond, to an imine and t-butyl iodosobenzene. The imine, in turn, undergoes hydrolysis to the aldehyde. Indeed, our studies with diverse α-amino acid systems show that this is the preferred pathway with reagent (1) (CHART C.11). An important point that has to be taken note of in the oxidation of amines with reagent (1) is that, unlike those where either a C-C π bond is cleaved or oxidized, or as in the case of oxidation of aralkyl substrates where optimum conditions required heating at 140° in chlorobenzene, the amine oxidations can be effectively achieved at room temperature or below, either supported on silica gel or otherwise.

In addition to the illustration of the utility of 4-^{t}butyl iodoxybenzene as a reagent in terms of five distinct reactions types, vide supra, the present work also contains the transformation of other functional groups with (1) such as sulfides, alcoholic function, enamines and others.

A Study of the Reaction of 4-^{t}Butyl Iodoxybenzene (1) with Protected and Free Coded α-Amino Acids

Background

An aspect that is under investigation in the laboratory where this work is being reported is the site-specific, group-specific transformation of the side chains of coded α-amino acids. An approach that has received considerable attention is to bring about such changes by oxidative procedures, since, in principle, 13 of the coded 20 amino acids have side chains that are susceptible to oxidation. Having established the utility of 4-^{t}butyl iodoxybenzene as an oxidizing agent, it was considered logical to examine the scope of reagent(1) in bringing about oxidative transformations of coded α-amino acid side chains. In addition to demonstrate the ability of reagent (1) to bring about oxidation of the amino functionality of α-amino acids, the oxidative transformations of few coded α-amino acid esters were also examined. All the amino acid substrates used in the present work were prepared by known procedures and by normal methods used in amino acid chemistry.

N-Benzoyl-L-methionine methyl ester (4)[69] was reacted with 1.5 equivalents of 4-^{t}butyl iodoxybenzene (1) in chlorobenzene at 140^{o} for 3.5 h. The products were separated into neutral and acidic fractions. The neutral fraction, on careful chromatography over silica gel, gave compounds 5, 6 and 7 to which, based on spectral and analytical data, are assigned

CHART C.12

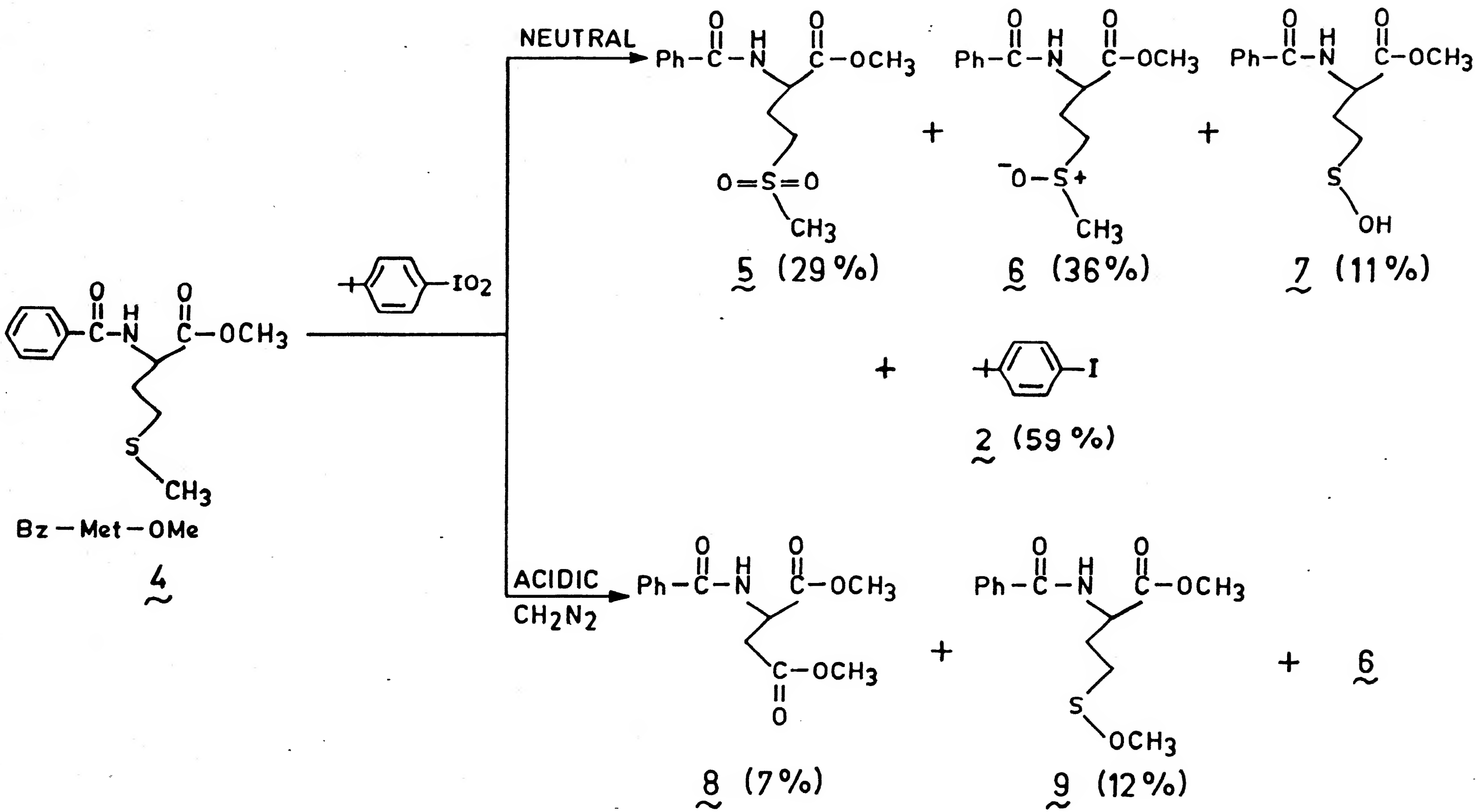
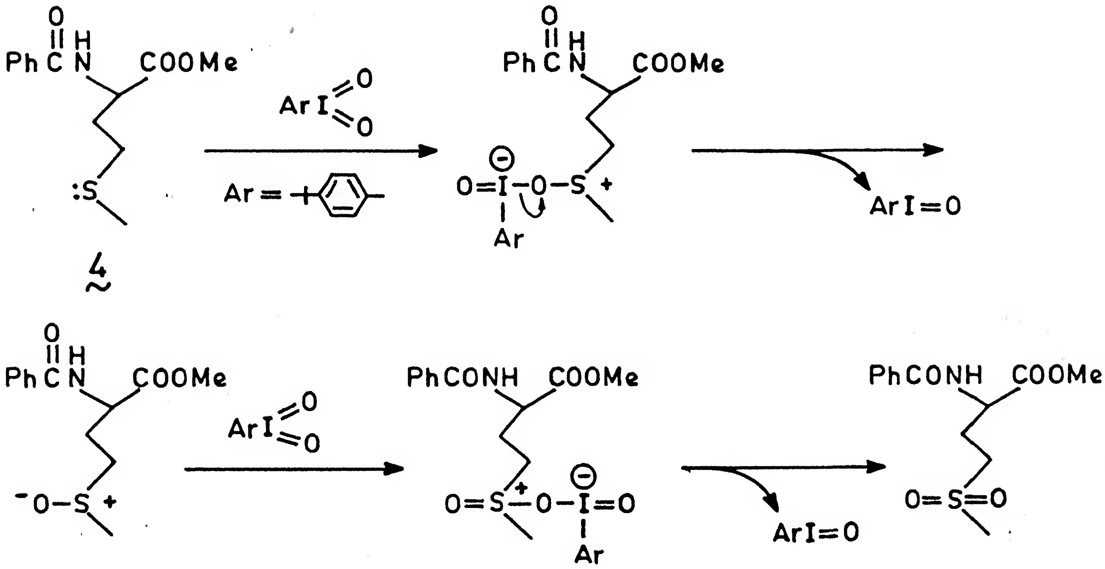
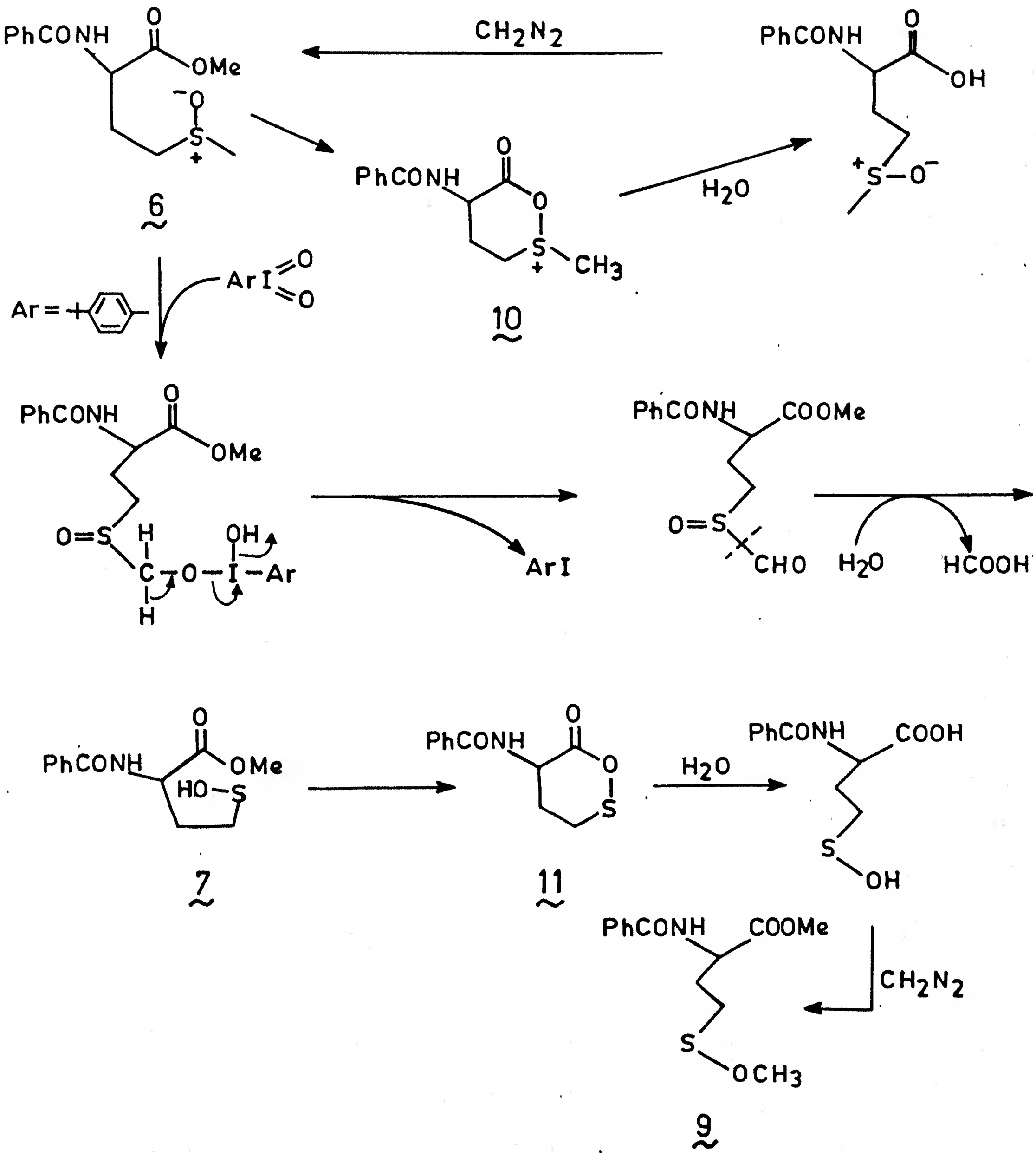


CHART C.13



4
6
5

CHART C.14


PhCONH
OMe
CH2N2
OH
H2O
CH3
Ar=
ArI
COOMe
CHO
HCOOH
HO–S
COOH
OCH3
6
10
7
11
9

10 from further oxidation. Indeed, the isolation of compound 9 which is a further esterified product of 7, in the bicarbonate layer, could again be explained on the basis of a cyclic intermediate such as 11, which would undergo opening to the carboxylic acid that would stay in the bicarbonate layer. Thus, the envisaged intermediates 10 and 11 (CHART C.14) would account for the same or similar products isolated from the neutral as well as acidic fractions. The possibilities that the compounds are partially taken up in the bicarbonate is highly unlikely from solubility studies of products isolated from the neutral fraction. CHART C.15 rationalizes the formation of the aspartic acid 8. It is envisaged that the sulfone 5 could undergo the Type IV reaction of 4-^{t}butyl iodoxybenzene leading to the carbonyl intermediate 12 (CHART C.15), which could undergo hydrolysis to L-aspartic acid α-methyl ester, which, in turn, with diazomethane, would lead to compound 8.

5: mp : 106 °C.

ir : ν_{max} (KBr) cm^{-1}: 3300 (NH), 1730 (C=O), 1630, 1290, 1230, 1120 (SO_2).

nmr : δ ($CDCl_3$), 60 MHz: 2.9 (s, 3 H, $SO_2C\underline{H}_3$), 3.0-3.41 (m, 4 H, $-C\underline{H}_2-C\underline{H}_2-$), 3.75 (s, 3 H, $COOC\underline{H}_3$), 4.9 (q, 1 H, tert-proton), 7.1-7.9 (m, 5 H, aromatic).

m/z : 299 (M^+), 240 (M^+ - COOMe), 194 (M^+ - COPh).

6: ir : ν_{max} (neat) cm^{-1}: 3300 (NH), 1730 (C=O), 1635, 1220, 1030 (sulfoxide).

nmr : $\delta(CDCl_3)$, 60 MHz: 2.56 (s, 3 H, $SOC\underline{H}_3$), 2.63-3.10 (m, 4 H, $-C\underline{H}_2C\underline{H}_2-$), 3.73 (s, 3 H, $COOC\underline{H}_3$), 4.85 (q, 1 H, tert-proton), 7.3-8.0 (m, 5 H, aromatic).

m/z : 283 (M^+), 284 (M^+ + 1).

7: mp : 132°C.

ir : ν_{max} (KBr) cm^{-1}: 3300 (NH), 1725 (C=O), 1525, 1240, 1030, 700.

nmr : $\delta(CDCl_3)$, 60 MHz: 2.8-3.25 (m, 4 H, $-C\underline{H}_2C\underline{H}_2-$), 3.8 (s, 3 H, $COOC\underline{H}_3$), 4.9 (q, 1 H, tert-proton), 7.20-8.12 (m, 5 H, aromatic).

m/z : 269 (M^+).

8: ir : ν_{max} (neat) cm^{-1}: 3320 (NH), 1725 (ester), 1670, 1470.

nmr : $\delta(CDCl_3)$, 60 MHz: 2.85-3.1 (m, 2 H, $-C\underline{H}_2$), 3.6 (s, 3 H, β-$COOC\underline{H}_3$), 3.7 (s, 3 H, α-$COOC\underline{H}_3$), 4.82 (q, 1 H, tert-proton), 7.2-8.0 (m, 5 H, aromatic).

9: ir : ν_{max} (neat) cm^{-1}: 3400 (NH), 1730 (ester), 1667, 1535, 1235, 1010, 725.

nmr : $\delta(CDCl_3)$, 60 MHz: 2.53 (s, 3 H, S-$OC\underline{H}_3$), 2.62-3.17 (m, 4 H, $-(C\underline{H}_2)_2$), 3.73 (s, 3 H, $COOC\underline{H}_3$), 4.8 (q, 1 H, tert-proton), 7.3-8.07 (m, 5 H, aromatic).

m/z : 283 (M^+), 284 (M^+ + 1).

Parenthetically, the possible involvement of 4-^{t}butyl iodosobenzene, envisaged in CHART C.13, in further transformations to products observed, can not be completely ruled out.

The reaction of N-benzyloxycarbonyl-L-methionine methyl ester[69] (13) with nearly 1 equivalent of the reagent (1) in chlorobenzene at 140^{o} for 2.5 h was found to be much less complicated and workup involving chromatography led to the isolation of the sulfone 14 (57%) which is very closely related to 5 and benzyl carbamate arising from elimination (36%). The reaction also led to the recovery of the reagent in the form of 4-^{t}butyl iodobenzene in 72% yields which could be recycled. Surprisingly, no acidic product was encountered in this reaction. The formation of 15 is noteworthy in that it is obtained in relatively high yields (36%). It is possible that the formation of this product, arising from elimination, is greatly promoted by intermediate such as 16 (CHART C.16).

14: mp : $89^{o}C$.

ir : ν_{max} (KBr) cm^{-1}: 3310 (NH), 1725, 1680 (C=O), 1520, 1310, 1240, 1120 (SO_2).

nmr : δ ($CDCl_3$), 60 MHz: 2.38 (m, 2 H, $-CH_2C\underline{H}_2-CH$), 2.88 (s, 3 H, $SO_2C\underline{H}_3$), 2.93-3.38 (m, 2 H, $-CH_2C\underline{H}_2SO_2Me$), 3.76 (s, 3 H, $COOC\underline{H}_3$), 4.53 (m, 1 H, tert-proton), 5.09 (s, 2 H, $-OC\underline{H}_2Ph$), 5.78 (d, 1 H, $-N\underline{H}-CH-$), 7.31 (s, 5 H, aromatic).

m/z : 329 (M^{+}), 330 (M^{+} + 1).

CHART C.15

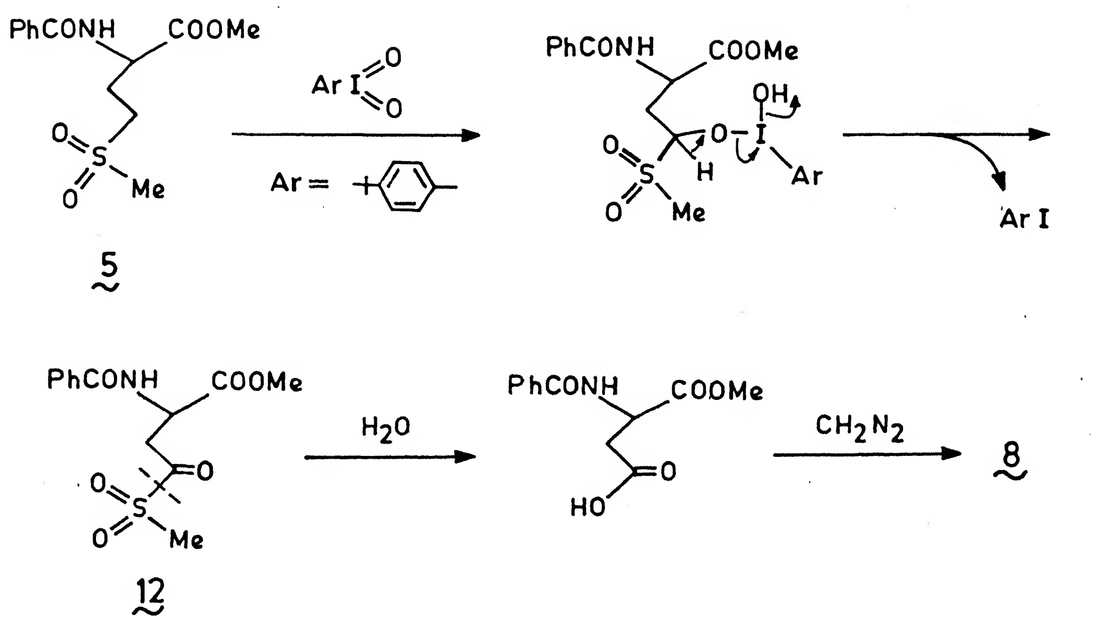
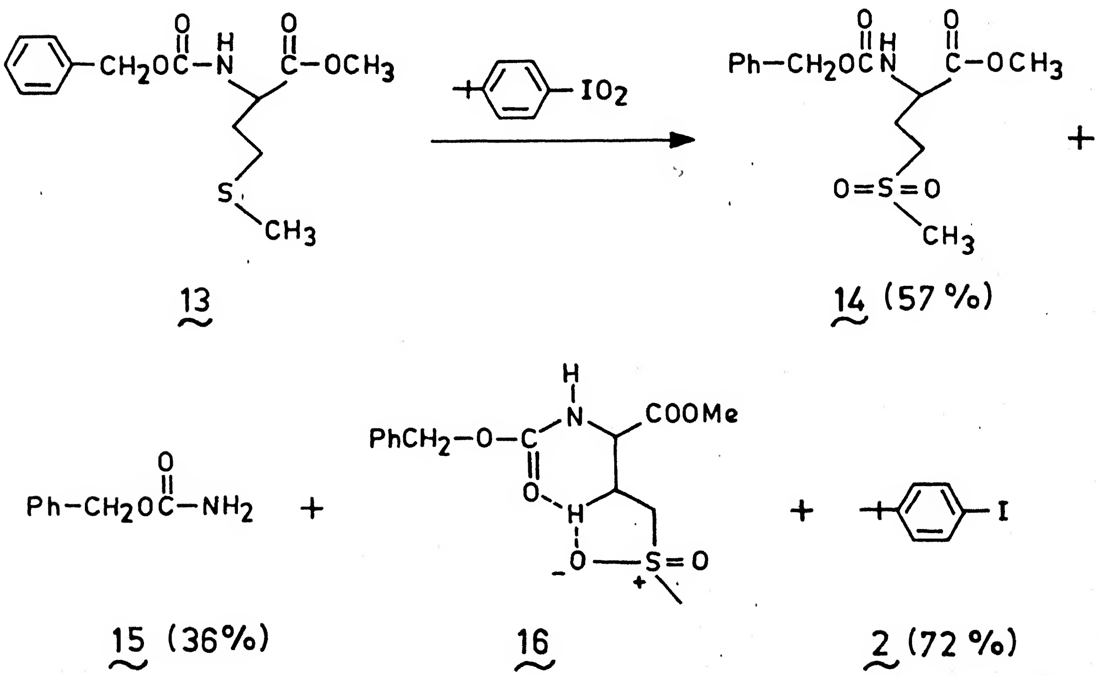


CHART C.16



15: mp : $84^{\circ}C$.

ir : ν_{max} (KBr) cm^{-1}: 3410, 3200, 1685.

nmr : $\delta(CDCl_3)$, 60 MHz: 5.13 (s, 2 H, $-OC\underline{H}_2Ph$), 7.32 (s, 5 H, aromatic).

m/z : 151 (M^+), 107 ($M^+ - CONH_2$).

The above experiments indicate that the major pathway in oxidations mediated with 4-^{t}butyl iodoxybenzene is the expected sulfur oxidation leading to sulfoxides and sulfones, in roughly the same order of yields. It was considered to be of interest whether this type of oxidation could be used in the transformation of the methionine side chain in peptides. With this objective, the dipeptide, namely benzyloxycarbonyl glycyl-methionine methyl ester (17) was prepared by accepted procedures as shown in CHART C.17. Compound 17, on reaction with 1.25 equivalents of the reagent (1), followed by workup, gave the sulfone 18 and the sulfoxide 19 in respectively 26% and 42% yields thus establishing that the peptide backbone is not affected in this oxidation. The structural assignments for 18 and 19 which are novel compounds are supported by spectral and analytical data (CHART C.17 & CHART C.18).

17: ir : ν_{max} (neat) cm^{-1}: 3350 (NH), 1740 (ester), 1680 (amide).

nmr : $\delta(CDCl_3)$, 60 MHz: 2.06 (s, 3 H, $SC\underline{H}_3$), 2.46 (m, 4 H, $-C\underline{H}_2C\underline{H}_2SCH_3$), 3.7 (s, 3 H, $-COOC\underline{H}_3$), 3.8–4.2 (m, 2 H, $NHC\underline{H}_2CO-$), 4.7 (d, 1 H, tert-proton), 5.1 (s, 2 H, $-OC\underline{H}_2Ph$), 5.67 (br, 2 H, $-N\underline{H}-$), 7.3 (s, 5 H, aromatic).

m/z : 354 (M^+), 355 ($M^+ + 1$).

18: ir : ν_{max} (neat) cm^{-1}: 3340 (br, NH), 1735 (ester), 1680 (amide), 1300, 1140 (SO_2).

nmr : $\delta(CDCl_3)$, 60 MHz: 2.83 (s, 3 H, $-SO_2C\underline{H}_3$), 2.92–3.44 (m, 4 H, $-CHC\underline{H}_2C\underline{H}_2SO_2-$), 3.7 (s, 3 H, $-COOC\underline{H}_3$), 3.77–4.72 (m, 3 H, $-C\underline{H}_2CONHC\underline{H}-$), 5.05 (s, 2 H, $-OC\underline{H}_2Ph$), 5.94 (br, 2 H, 2 x $N\underline{H}$), 7.26 (s, 5 H, aromatic).

m/z : 386 (M^+), 387 ($M^+ + 1$).

19: ir : ν_{max} (neat) cm^{-1}: 3320 (br, NH), 1740 (ester), 1670 (amide), 1045 (sulfoxide).

nmr : $\delta(CDCl_3)$, 60 MHz: 2.51 (s, 3 H, $-SOC\underline{H}_3$), 2.58–3.28 (m, 4 H, $-CHC\underline{H}_2CH_2SO-$), 3.7 (s, 3 H, $-COOC\underline{H}_3$), 3.88 (m, 2 H, $-NHC\underline{H}_2CO-$), 4.78 (m, 1 H, tert-proton), 5.08 (s, 2 H, $-OC\underline{H}_2Ph$), 5.98 (br, 2 H, 2 x $N\underline{H}$), 7.28 (s, 5 H, aromatic).

m/z : 370 (M^+).

CHART C.17

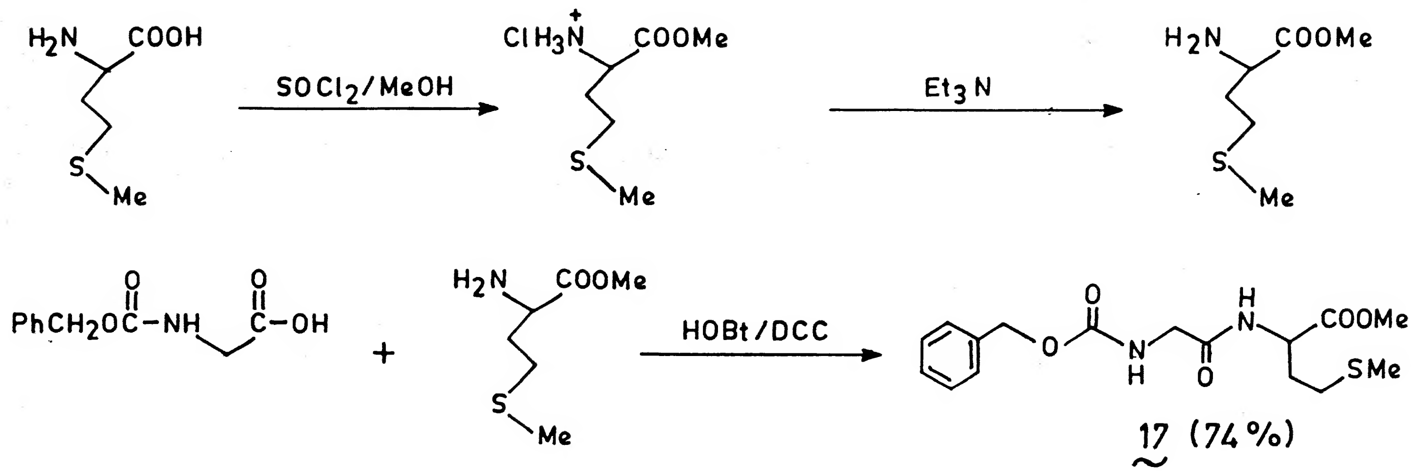
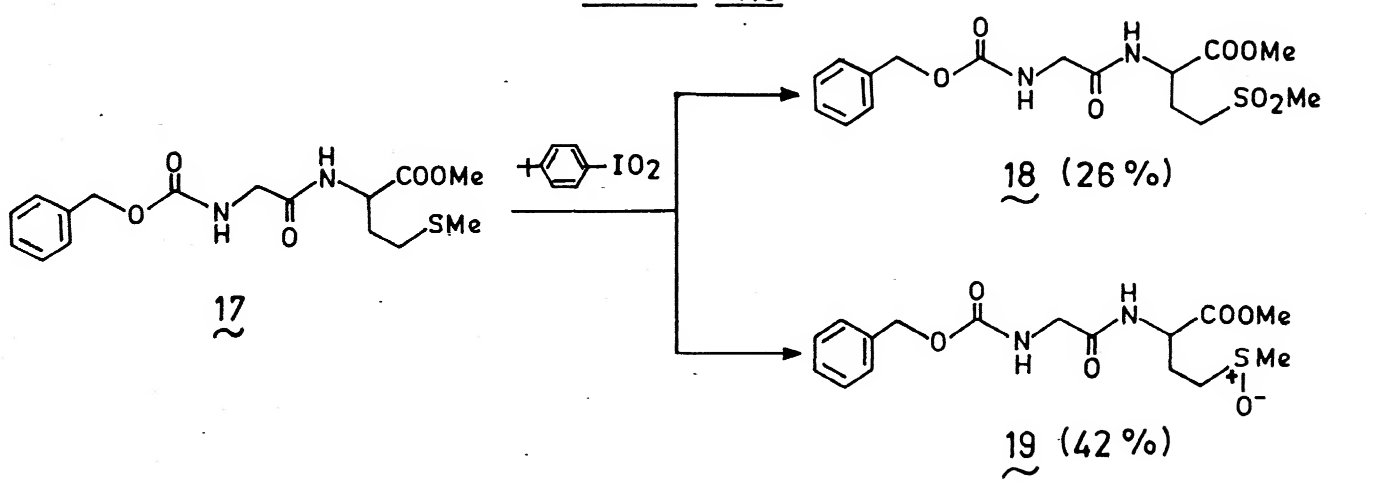


CHART C.18



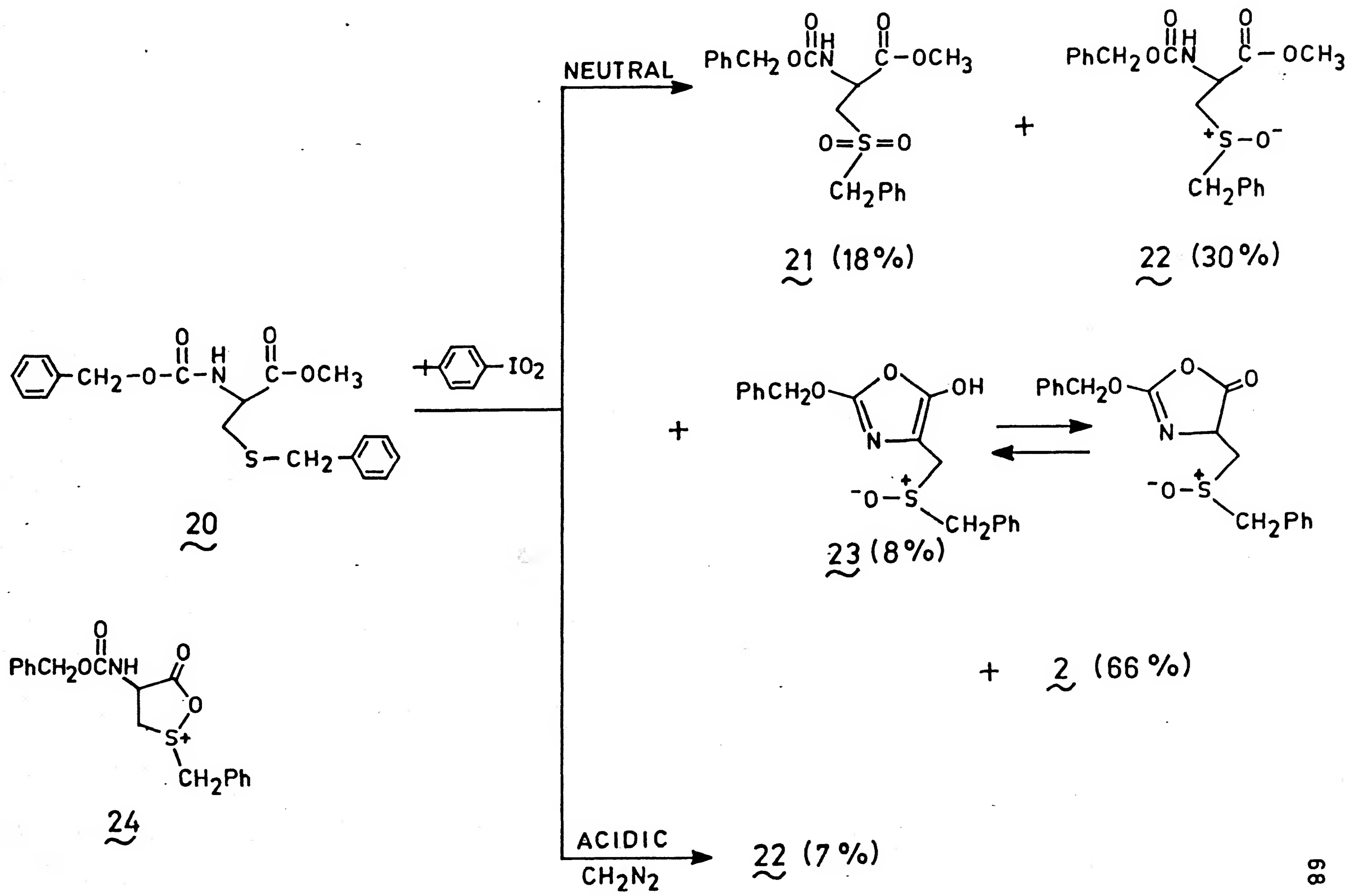
As the logical extension to the work reported above on methionine, oxidation with reagent (1) was also carried with N-benzyloxycarbonyl-S-benzyl-L-cysteine methyl ester[70] (20). Thus, the reaction of 20 with 1.5 equivalents of (1), under the general conditions, led to the isolation of the sulfone 21 and sulfoxide 22, in yields, respectively, 18% and 30%. 4-^{t}Butyl iodobenzene (2) was recovered in 66% yields. The structural assignments for 21 and 22 are supported by spectral and analytical data. In addition, there was also obtained compound, mp 112-114° which did not have the ester function (nmr). On the basis of spectral data, this compound is considered to be the azlactone 23 (CHART C.19). An interesting finding here was the observation that the acidic portion when esterified with diazomethane, gave a 7% yield of the sulfoxide 22 which tends to support the earlier rationalization pertaining to cyclic intermediates (vide supra) which, in this case, could be considered as 24 (CHART C.19).

21: mp : 174°C.

ir : ν_{max} (KBr) cm^{-1}: 3315 (NH), 1730 (ester), 1685, 1300, 1250, 1130 (SO_2), 1050.

nmr : δ ($CDCl_3$), 60 MHz: 3.5 (d, 2 H, $SO_2C\underline{H}_2CH$-), 3.71 (s, 3 H, $-COOC\underline{H}_3$), 4.2 (s, 2 H, $C\underline{H}_2Ph$), 4.72 (m, 1 H, tert-proton), 5.08 (s, 2 H, $OC\underline{H}_2Ph$), 5.9 (br, 1 H, $N\underline{H}$), 7.3 (s, 10 H, aromatic).

CHART C.19



m/z : 391 (M^+).

<u>22</u>: mp : 119-121°C.

ir : ν_{max} (KBr) cm^{-1}: 3310 (NH), 1730 (ester), 1685, 1265, 1030 (sulfoxide).

nmr : δ ($CDCl_3$), 60 MHz: 3.06 (d, 2 H, $-SOCH_2CH-$), 3.61 (s, 3 H, $-COOCH_3$), 3.91 (s, 2 H, $SOCH_2Ph$), 4.57 (br, 1 H, $-CH-$), 5.01 (s, 2 H, $-OCH_2Ph$), 6.11 (br, 1 H, $-NH-$), 7.2 (s, 10 H, aromatic).

m/z : 375 (M^+), 236 (M^+ - $SOCH_2Ph$).

<u>23</u>: mp : 112-114°C.

nmr : δ ($CDCl_3$), 60 MHz: 3.04 (m, 2 H, $SOCH_2-C{\lesssim}^{N}$), 3.93 (s, 2 H, $SOCH_2Ph$), 4.97 (s, 2 H, $-OCH_2Ph$), 7.2 (s, 10 H, aromatic).

An interesting property of 4-^{t}butyl iodoxybenzene was uncovered during endeavours to transform N-benzoyl-L-serine methyl ester (<u>25</u>) to oxidized products. The reaction of <u>25</u> with 1.5 equivalents of the reagent (<u>1</u>) in chlorobenzene at 140° for 6 h, gave the dehydroalanine (<u>26</u>) and benzamide, in yields, respectively, 55% and 34%. A 45% yield of 4-^{t}butyl iodobenzene was also obtained. No other products could be characterized in this reaction. A blank experiment, which excluded 4-^{t}butyl iodoxybenzene, even with prolonged heating for 10 h gave none of the dehydroalanine (<u>26</u>). Thus, the reagent (<u>1</u>) is involved

in same manner in the formation of the (26). Additionally, the absence of formation of benzamide in the blank reaction where the starting material was totally recovered would also suggest that even in the formation of benzamide which is an unusual elimination product reagent (1) is implicated. The transformation of (25) to (26) and benzamide is rationalized on CHART C.20. The formation of 4-^{t}butyl iodbenzene can be readily understood on the basis of the proven instability of this reagent, when not used, to fragment.

26: ir : ν_{max} (neat) cm^{-1}: 3398 (NH), 1710, 1670 (C=O).

nmr : δ ($CDCl_3$), 60 MHz: 3.8 (s, 3 H, $-COOC\underline{H}_3$), 5.9, 6.7 (br, br, 1 H, 1 H, olefin), 7.1-7.9 (m, 5 H, aromatic), 8.4 (br, 1 H, -N$\underline{H}$-).

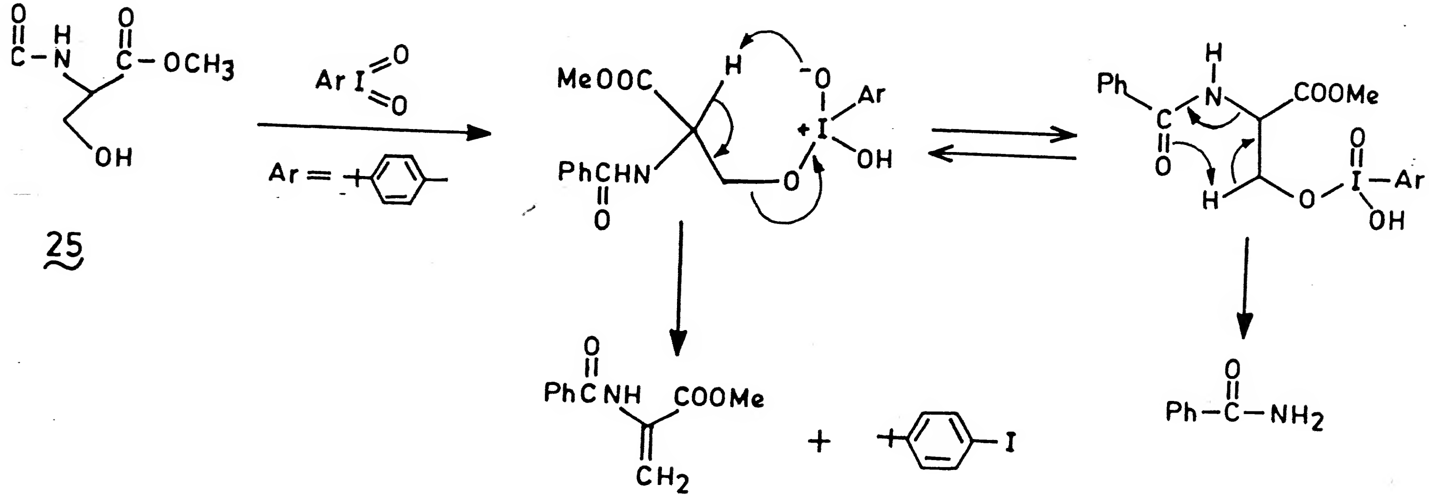
m/z : 205 (M^+), 206 (M^+ + 1), 146 (M^+ - COOMe).

Earlier studies have established that 4-^{t}butyl iodoxybenzene has a reaction profile which is quite similar to that of ozone. It was, therefore, considered very interesting and important to study the behaviour of 4-^{t}butyl iodoxybenzene (1) towards the three coded amino acids that carry aromatic side chains, namely, phenylalanine, histidine and tryptophan, not only with a view to delineate the pathways involved in such oxidations, if any, but also to assess the practical utility of the

reagent (1) with reference to transformation of amino acids and peptides that carry side chains possessing an aromatic unit. It was also considered to be of interest to compare the results of such a study, with the results obtained from oxidation of such amino acids with other oxidising agents that are being currently pursued in this laboratory. In the event, the reaction of N-benzoyl-L-phenylalanine methyl ester[71] with 1.5 equivalents of reagent (1) in chlorobenzene at 140° for 8 h gave 14% of N-benzoyl-L-aspartic acid α-methyl ester which was esterified with diazomethane to 8 and found identical with an authentic sample. Thus, the potential of 4-^{t}-butyl iodoxybenzene to transform a phenyl ring to a carboxylic residue has been established although its efficacy is moderate, since about 60% of the starting material was recovered unchanged. Nevertheless when viewed in the light of the fact that there are very few reagents which can bring about the oxidation of a phenyl ring, the (27) to (8) transformation should be considered important. This reaction also led to the isolation of 2 in 81% yields. Another noteworthy feature of this oxidation is that even though N-benzoyl-L-phenylalanine methyl ester (27) possesses two aromatic moieties, the side chain phenyl alone is oxidized on treatment with (1). This is also the case with other oxidizing agents such as ruthenium tetraoxide (CHART C.21).

The reaction of N-benzyloxycarbonyl-L-histidine methyl ester[72] (28) with 4-^{t}butyl iodoxybenzene gave very interesting

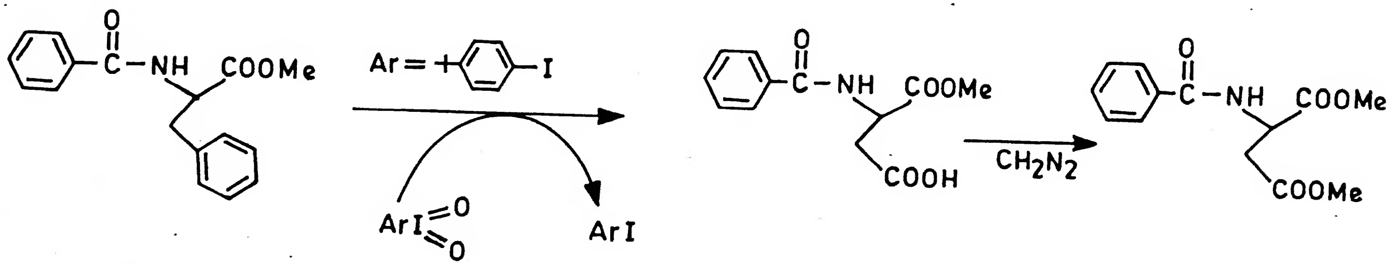
CHART C.20



25

26 (55%) + 2 (45%) (34%)

CHART C.21



27 1 2 (81%) 8 (14%)

results. Thus, when equivalent amounts of (28) and (1) in chlorobenzene was held at 140° for 7 h and worked up, there was obtained the unusual product (29), mp 175° in 38% yield, and a 30% yield of benzylcarbamate (CHART C.22). In addition, there was also obtained 64% of 4-^{t}butyl iodobenzene (2). The acidic portion yielded no products. Thus, under the conditions outlined above, the reaction was clean, gave a single product from the histidine moiety oxidation.

The formation of 29 from 28 is rationalized in CHART C.23. It is envisaged that the initial interaction leads to the oxidation of the 4-imidazole position and eventual hydroxylation. The 4-hydroxy imidazole thus generated undergoes prototropic shifts and hydrolysis leading to the observed product (CHART C.23).

28: ir : ν_{max} (neat) cm^{-1}: 3300 (br, NH), 1720 (ester), 1440, 1215.

nmr : δ ($CDCl_3$), 60 MHz: 3.07 (d, 2 H, $-C\underline{H}_2CH-$), 3.62 (s, 3 H, $-COOC\underline{H}_3$), 4.57 (m, 1 H, tert-proton), 5.02 (s, 2 H, $-OC\underline{H}_2Ph$), 6.27 (d, 2 H, 2 x$N\underline{H}-$), 7.12-8.02 (m, 7 H, aromatic olefin).

29: mp : 175°C.

ir : ν_{max} (KBr) cm^{-1}: 3320 (NH), 1750 (ester), 1725 (CHO), 1695 (amide).

nmr : δ ($CDCl_3$), 60 Mhz: 3.12 (m, 2 H, $-CHC\underline{H}_2CH-$), 3.7 (s, 3 H, $-COOC\underline{H}_3$), 4.42 (m, 2 H, 2 x$C\underline{H}-$),

CHART C.22

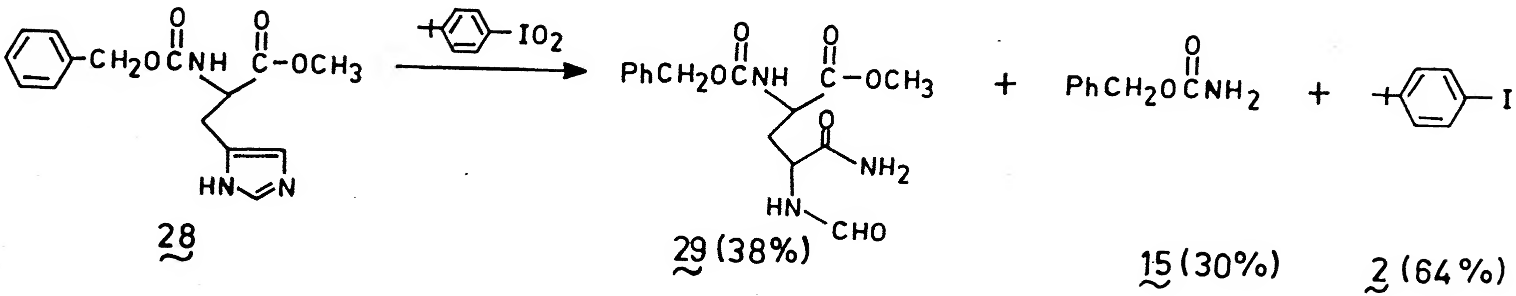
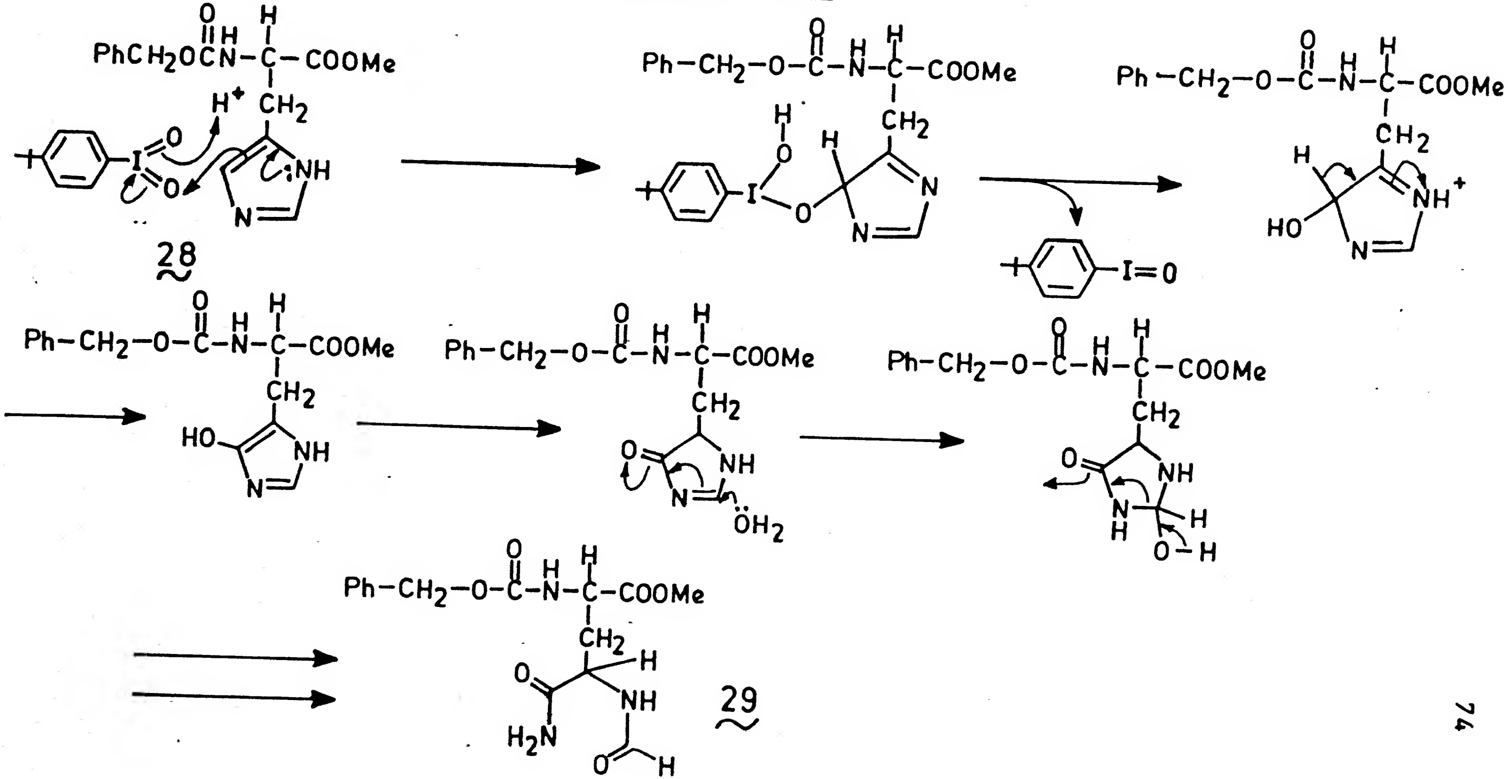


CHART C.23



5.07 (s, 2 H, $-OC\underline{H}_2Ph$), 5.6 (br, 2 H, $-CON\underline{H}_2$), 6.71 (br, 2 H, 2 x$N\underline{H}-$), 7.28 (s, 5 H, aromatic), 8.16 (s, 1 H, $-C\underline{H}O$).

m/z : 337 (M^+), 278 (M^+ - COOMe), 246 (M^+ - CH_2Ph).

The reaction of N-benzoyl-L-tryptophan methyl ester[73] (30) with 1.5 equivalent of the reagent (1) at 140° for 1.5 h, followed by the usual workup, gave 70% yield of the formylkynurenine (31) whose formation could be readily understood on the basis of adduct (32) which is precisely that could be anticipated on reaction of 30 with ozone. About 15% of the starting material was recovered in this reaction. To the best of our knowledge, the 30 to 31 transformation mediated by 4-^{t}butyl iodoxybenzene is the best procedure for the preparation of 31 (CHART C.24). Further, the chirality in this transformation was retained. This was demonstrated *via* further transformation of this compound to aspartic acid and comparison of the optical rotation with that of an authentic sample. This reaction gave no acidic product.

30: mp : 109-111 °C.

ir : ν_{max} (KBr) cm^{-1}: 3320 (NH), 1720 (ester), 1620, 1595.

nmr : δ ($CDCl_3$), 60 MHz: 3.4 (d, 2 H, methylene proton), 3.65 (s, 3 H, $-COOC\underline{H}_3$), 5.1 (m, 1 H, tert-proton),

6.6-7.9 (m, 11 H, aromatic), 8.65 (br, 1 H, -NH-).

31: mp : 94-95°C.

ir : ν_{max} (KBr) cm^{-1}: 3310 (NH), 1750 (-COOMe), 1730 (> C=O).

nmr : δ ($CDCl_3$), 60 MHz: 3.85 (s + d, 5 H, $-COOCH_3$, methylene proton), 5.15 (m, 1H, tert-proton), 7.05-8.05 (m, 9 H, aromatic), 8.65 (br, 2 H, -NHCHO, -NHCOPh), 11.3 (br, 1 H, CHO).

m/z : 354 (M^+).

A reaction that has been observed in this laboratory and by others is the oxidation of N-benzoy-L-proline methyl ester[74] at the five position by RuO_4. It was therefore considered interesting to study the reaction of N-benzoyl-L-proline methyl ester (32) with reagent (1). In the event, the reaction of (32) with nearly equivalent amount of reagent (1) in chlorobenzene for 8 h followed by separation into neutral and acidic portions and the esterification of the product from the bicarbonate extract, gave a 14% of N-benzoyl glutamic acid dimethyl ester (33), which was compared with an authentic sample. The neutral extract afforded on chromatography unchanged starting material and 4-^{t}butyl iodobenzene (75%). The formation of (33) from oxidation of (32) is rationalized in CHART C.25. The primary step is envisaged as Type IV process encountered with

4-^{t}butyl iodoxybenzene (<u>vide supra</u>) and the collapse of this intermediate to the iodoso compound and the oxidized substrate which is designated as (<u>34</u>) in CHART C.25. Compound <u>34</u> is actually, N-benzoyl pyroglutamic acid methyl ester which is known to hydrolyse readily to the corresponding glutamic acid, diazomethane esterification then would give rise to observed product (<u>33</u>).

<u>32</u>: mp : 88-89^{o}C

ir : ν_{max} (KBr) cm^{-1}: 1732 (ester), 1618, 1410, 1200, 1180.

nmr : δ ($CDCl_3$), 60 MHz: 1.38-2.83 (m, 6 H, $-(CH_2)_3-$), 3.78 (s, 3 H, $-COOC\underline{H}_3$), 4.68 (m, 1 H, tert-proton), 7.4 (m, 5 H, aromatic).

<u>33</u>: ir : ν_{max} (neat) cm^{-1}: 3340 (br, NH), 1660 (C=O).

nmr : δ ($CDCl_3$), 60 MHz: 2.04 (m, 4 H, $-C\underline{H}_2C\underline{H}_2COOMe$), 3.61 (s, 3 H, γ-$COOC\underline{H}_3$), 3.73 (s, 3 H, α-$COOC\underline{H}_3$), 4.82 (m, 1 H, tert-proton), 7.12-7.52 (m, 5 H, aromatic).

m/z : 279 (M^+), 220 ($M^+ - COOCH_3$).

The transformation of aniline to azobenzene with 4-^{t}butyl iodoxybenzene was described earlier and was referred to as the Type V reaction that could be brought about with reagent (<u>1</u>). In the present work, the reaction of amino acid esters with (<u>1</u>)

CHART C.24

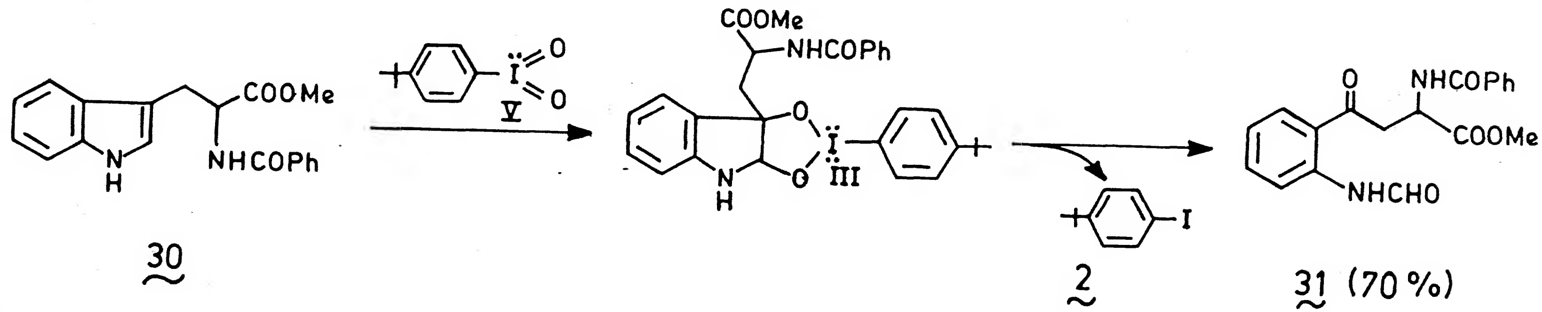
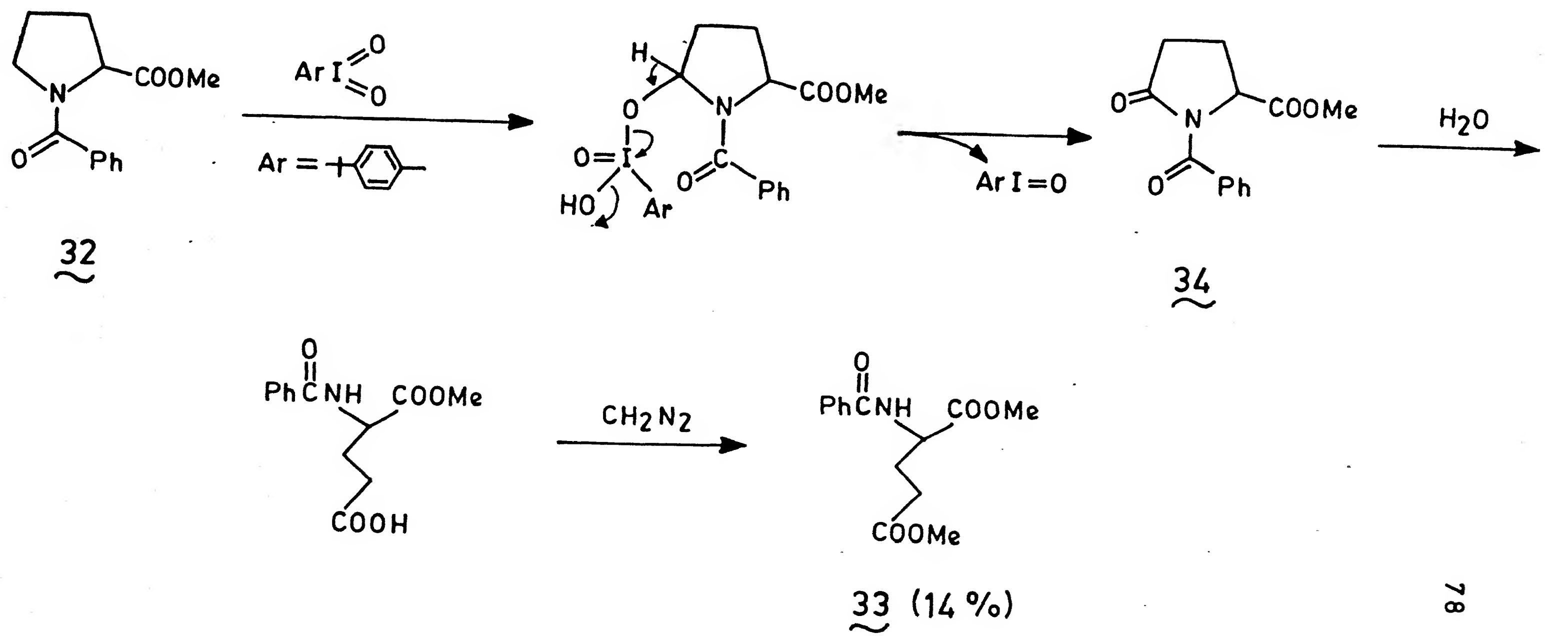


CHART C.25



has been explored to compare such results with that observed earlier. Additionally, the oxidation of free amino acids, particularly aromatic amino acids like phenylalanine and tryptophan is one of the most important biogenetic pathways, involving these compounds. In the event, the reaction of L-phenylalanine methyl ester with 1.25 equivalents of 4-^{t}butyl iodoxybenzene (1) in chlorobenzene at 140^o for 5 h led to, after chromatography, the isolation of compounds which have been assigned tentatively on the basis of spectral data, structures (36) and (37). The workup also afforded 77% of 4-^{t}butyl iodobenzene (2). The yields of (36) and (37) obtained are respectively 25% and 32% (CHART C.26). The formation of 2,4-diphenyl 3,5-dicarbomethoxy pyrrole (36) is rationalized in CHART C.27. As in several previous cases, the initial interaction leads to the oxidation of the primary amine function to an imine unit which readily tautomerizes to an enamine. This key enamine intermediate is envisaged to undergo loss of ammonia to give phenyl propiolic acid methyl ester which accepts the precursor enamine in a Michael type of addition. Cyclization followed by oxidation would give rise to compound 36 (CHART C.27). The formation of compound 37 is rationalized in CHART C.28. This complex change is envisaged as taking place *via* further oxidation of the enamine intermediate referred to in CHART C.27 to an azo compound *via* pathways similar to that involved in the transformation of aniline to azobenzene. Electrocyclic reaction

CHART C.26

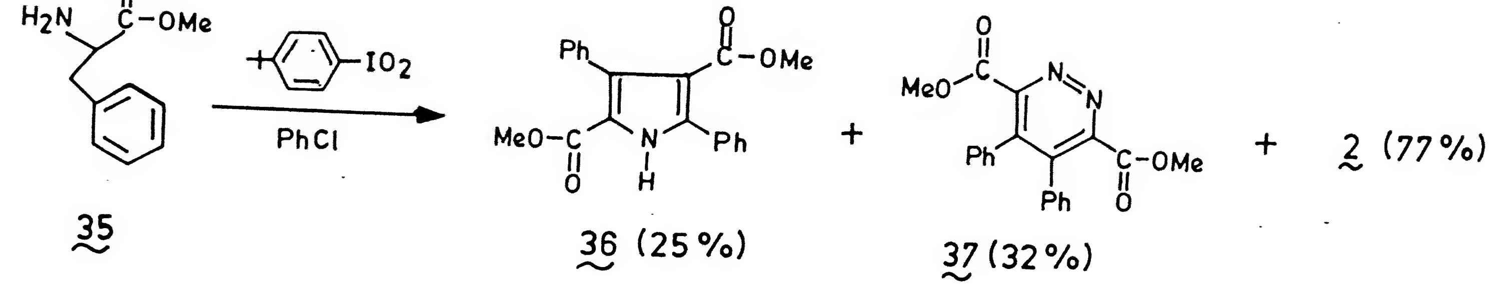
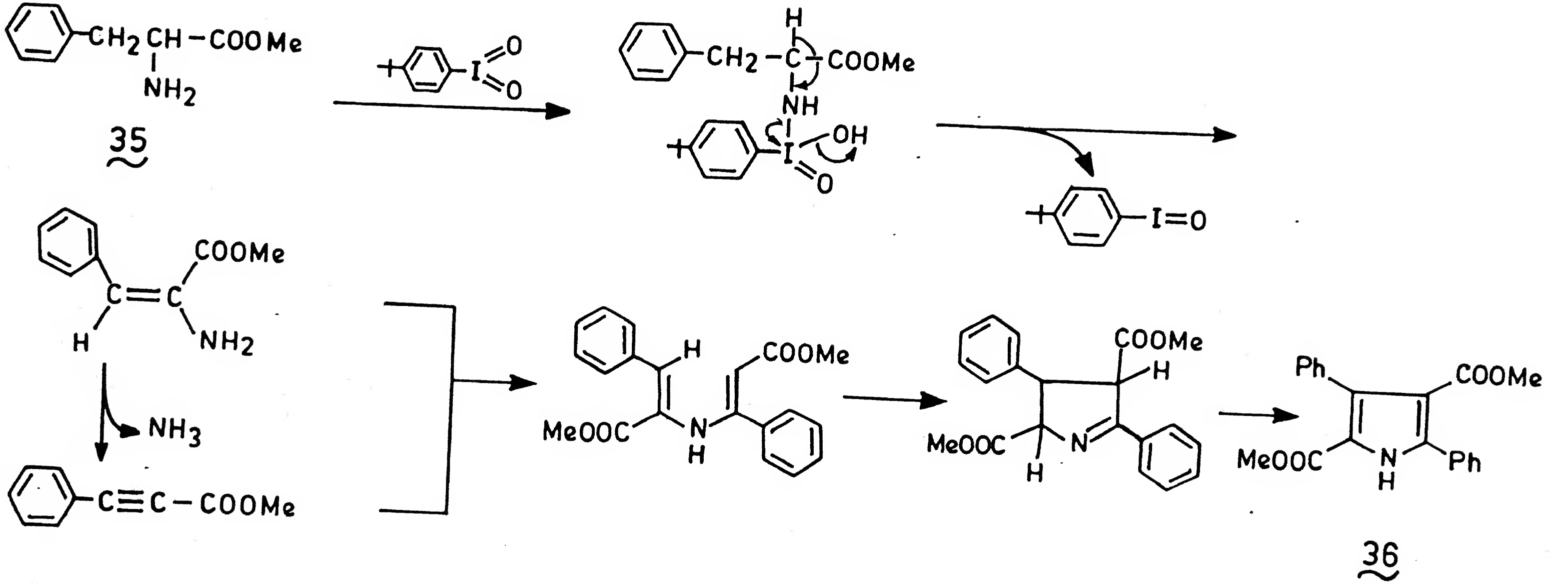


CHART C.27



of this azo compound followed by oxidation would lead to 37 (CHART C.28).

36: ir : ν_{max} (neat) cm^{-1}: 3440 (NH), 1730 (br, ester).

nmr : δ ($CDCl_3$), 60 MHz: 3.73 (s, 6 H, 2 x$COOC\underline{H}_3$), 7.2 (m, 10 H, aromatic), 8.2 (br, 1 H, -N$\underline{H}$).

m/z : 335 (M^+), 336 (M^+ + 1).

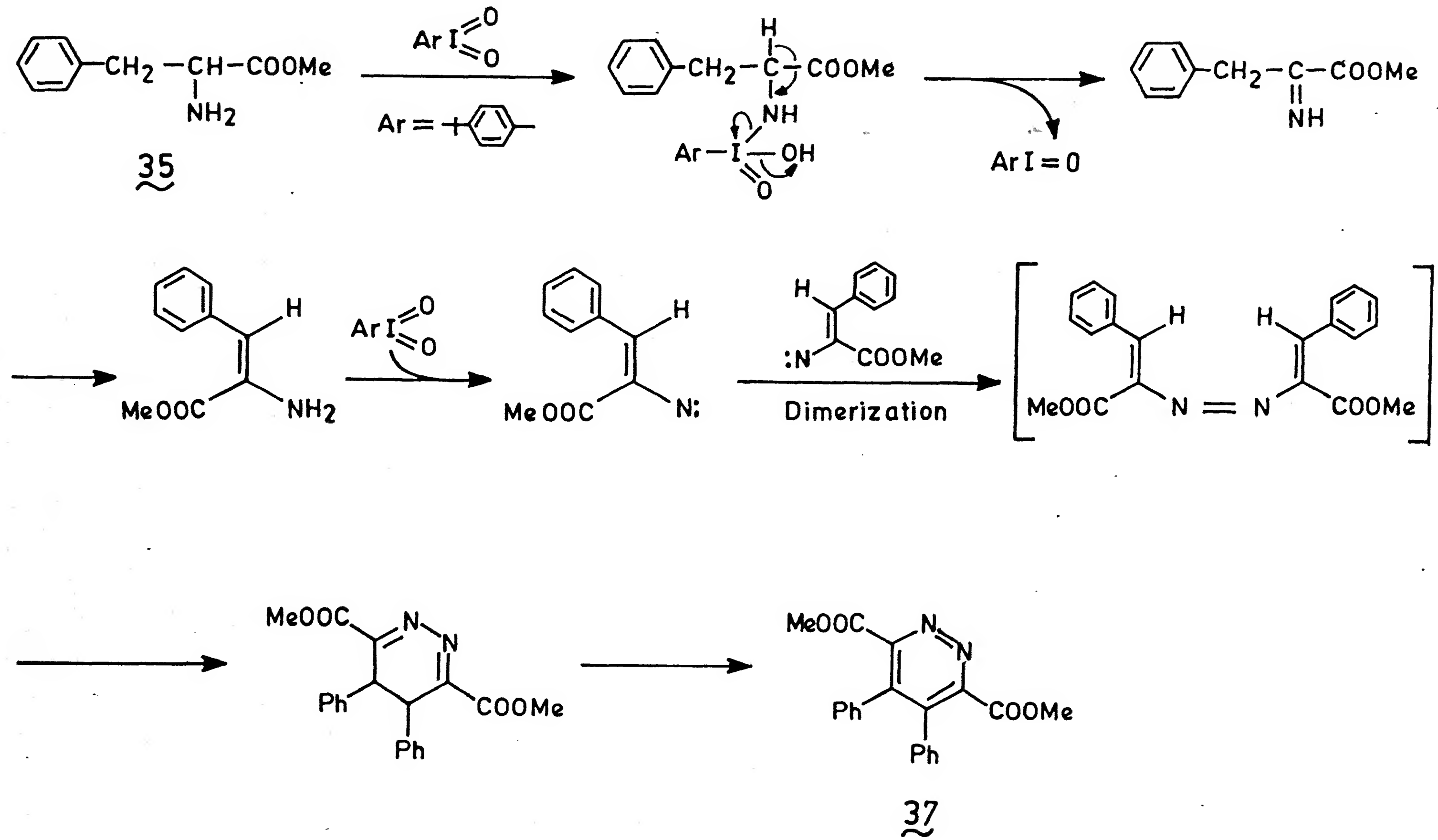
37: ir : ν_{max} (neat) cm^{-1}: 1740 (ester).

nmr : δ ($CDCl_3$), 60 MHz: 3.76 (s, 3 H, -$COOC\underline{H}_3$), 3.8 (s, 3 H, -$COOC\underline{H}_3$), 6.87-7.68 (m, 10 H, aromatic)

m/z : 348 (M^+).

A remarkable transformation was observed when L-tryptophan methyl ester (38) was left stirred in benzene with half an equivalent of 4-^{t}butyl iodoxybenzene in benzene at room temperature for 1.5 h. Evaporation of solvents followed by chromatography gave, besides 71% of 4-^{t}butyl iodobenzene (2), a reddish crystalline compound, mp 197°, to which structure (39) has been assigned on the basis of nmr which clearly showed the compound did not possess any nonaromatic type protons. Additionally, the mass spectrum of this compound was in agreement with assignment (39). The formation of (39) so readily from (38) with (1) in benzene at room temperature is rationalized in CHART C.29. It is envisaged that the

CHART C.28



primary enamine oxidation product undergoes hydrolysis and cyclization leading to (<u>39</u>). The structure of this product as well as pathways of oxidation of <u>38</u> under usual conditions awaits further exploration.

<u>39</u>: mp : $197^{\circ}C$.

ir : ν_{max} (KBr) cm^{-1}: 3300 (br, NH), 1670 (br, C=O).

nmr : δ ($CDCl_3$), 60 MHz: 7.08-7.49 (m, 2 H), 7.58 (s, 1 H), 7.88-8.18 (m + d, 2 H), 8.78 (m, 1 H, -N<u>H</u>).

m/z : 185 (M^+).

The above account provides a summary of reactions thus far carried out with 4-^{t}butyl iodoxybenzene (<u>1</u>). Reagent (<u>1</u>) has been demonstrated to bring about oxidative transformations that can be classified into five types. The reaction of protected sulfur-containing coded amino acids, namely, methionine and cysteine affords largely a mixture of sulfoxide and sulfone. The formation of other products in these reactions, particularly, the degradation of methionine side chain to that of an acetic acid is of interest. Convincing evidence for a participation of 4-^{t}butyl iodoxybenzene in elimination has been brought out by studies on benzoyl-L-serine methyl ester. A very important result is the degradation of benzoyl-L-phenylalanine methyl ester to L-aspartic acid involving the degradation of the aromatic ring of the side chain to a carboxyl unit. In the

case of benzyloxycarbonyl-L-histidine methyl ester, the oxidation proceeds via hydroxylation of the imidazole nucleus. A result that could have some practical application is the oxidation of benzoyl-L-tryptophan methyl ester to Kynurenine (31) in 70% yields. N-Benzoyl-L-proline methyl ester is oxidized with (1) to a pyroglutamic acid intermediate. The reaction of (1) with unprotected amino acid esters was complex and the pathways were not predictable and the assignment of unusual structures (36), (37) and (39) merits further confirmation. The most notable aspect of the present endeavour is the demonstrated capability of (1) to bring about the oxidative transformation of a variety of substrates via a variety of mechanistic pathways. Further work along the lines developed here would hopefully lead to practical application of (1) in chemical transformations. The present work also involves a very preliminary examination of the use of 4-^{t}butylbenzene iododichloride (3) as a reagent. It has been found that the reactivity pattern is as expected, similar to that of the parent system, namely, phenyl iododichloride. The pronounced enhanced solubility of 3 in solvents such as benzene gives it a distinct advantage over the parent system. As illustrated in CHART C.30 compound (3) transforms benzylamine, cyclohexanone oxime and camphene to, respectively, benzaldehyde, cyclohexanone and bornanedichloride via pathways which have been described in Section B.

CHART C.29

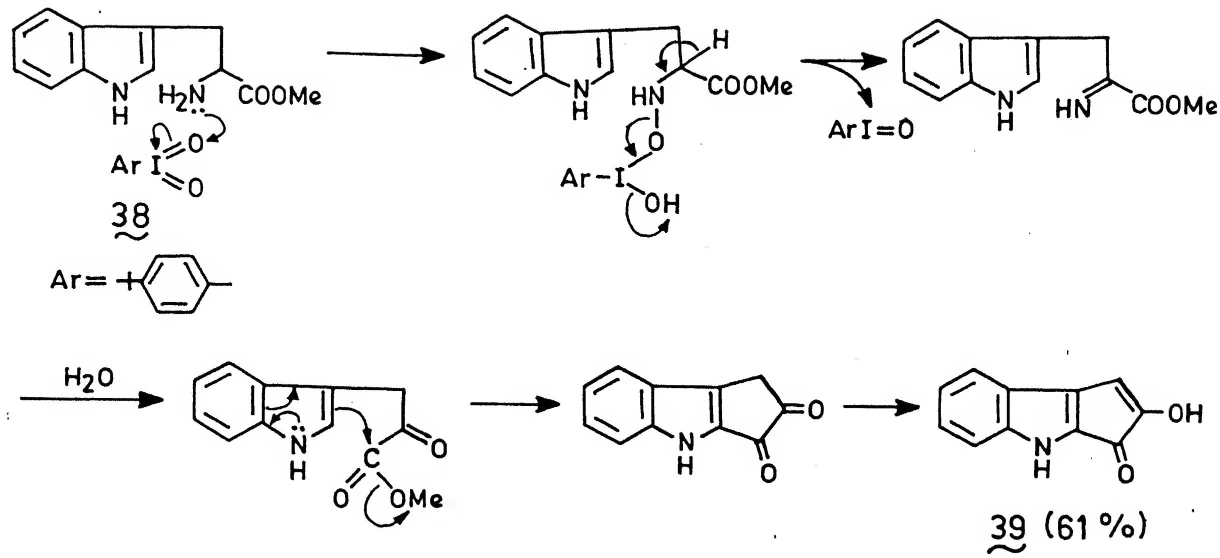
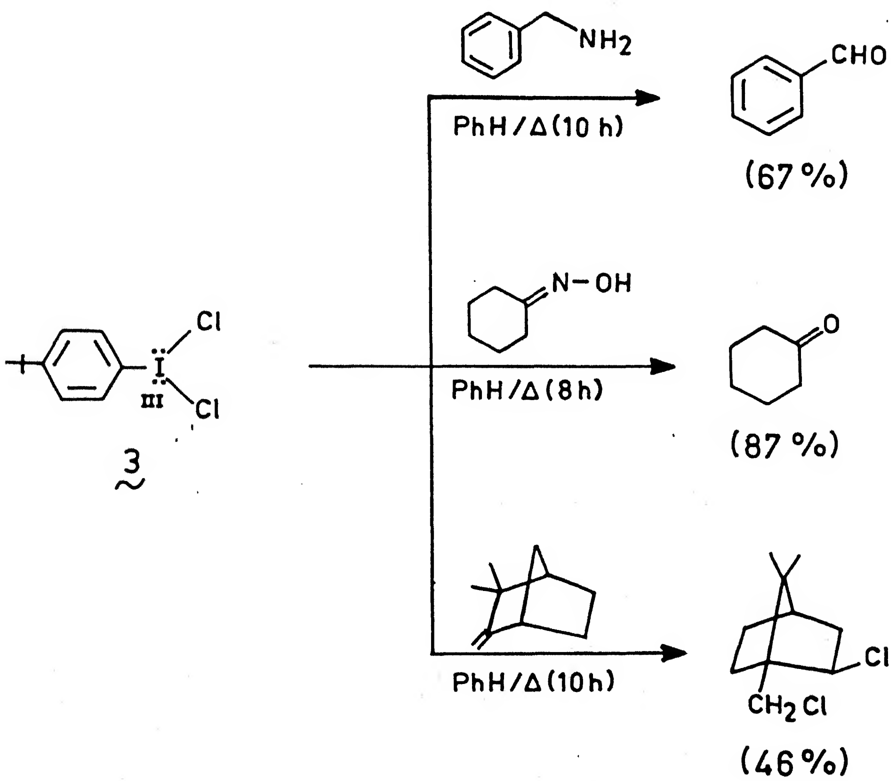


CHART C.30



By a fortunate coincidence, whilst the work on iodoxybenzene and appropriately substituted iodoxybenzene was in progress with respect to their possible utilization as ozone equivalents and in other oxygen transfer processes, endeavours were on way to explore and exploit the full potential of nitroethylene (40) as a reagent in organic chemistry. The wide scale application of nitroethylene is impeded by two factors, namely, the difficulties associated with storage of this reagent and the fact that its preparation hitherto involve the use of nitromethane as the starting material. With reference to the first problem, it was satisfactorily solved in this laboratory by the preparation of the tailor-made reagent, 2-nitroethyl phenyl sulfoxide (41). It was found that this reagent, under mild thermal conditions, readily fragments via a Cope-type of transition state to nitroethylene as illustrated in CHART C.31. An interesting problem arose during the preparation of this transfer reagent, namely, the oxidation of 2-nitroethyl phenyl sulfide (42) to the sulfoxide (41) arising from the presence of a nitro-function. It was found that common oxidising agents like hydrogen peroxide and m-chloro perbenzoic acid gave complex products. However, the reagent iodoxybenzene that was being tested in the same laboratory was found to be exceptionally good to bring about the (42) to (41) oxidation in the presence of the nitro function. With the development 4-^{t}butyl iodoxybenzene as a much superior reagent to the parent, it was considered worthwhile to develop a method for the preparation of the nitro-

ethylene transfer reagent, 2-nitroethyl phenyl sulfoxide (41) without proceeding through nitromethane and incorporating reagent (1) in the (42) to (41) change. The problem with nitromethane is that its conjugate base has to be generated and then reacted with formaldehyde to 2-nitroethanol. This reaction is hazardous since it involves nitromethane anion. Further, the isolation of 2-nitroethanol is also very difficult. It was, therefore, concluded that any widely applicable method for the preparation of 2-nitroethyl phenyl sulfoxide (41) must not include nitromethane as the starting material. This problem now has been solved satisfactorily and the nitroethylene transfer agent (41) has been prepared by a novel strategy in the present work employing sodium nitrite to introduce the nitro-function and also incorporating the use of the relatively more soluble 4-^{t}butyl iodoxybenzene to bring about the facile and uncomplicated oxidation of 2-nitroethyl phenyl sulfide. The procedure for the preparation of 2-nitroethyl phenyl sulfoxide (41) from nitromethane is presented in CHART C-32.

Our present synthesis of 2-nitroethyl phenyl sulfoxide (41) starts from ethylene glycol, which, on reaction with HBr, is transformed to 2-bromoethanol in 30% yields. Reaction of this with the *in situ* generated thiophenol conjugate base gave 2-hydroxyethyl phenyl sulfide in 88% yields. Reaction of this with phosphorous tribromide gave the novel compound 2-bromoethyl phenyl sulfide (43) in 81% yields. Reaction of

2-bromoethyl phenyl sulfide with sodium nitrite in DMSO for 8 h at room temperature gave a 72% yield of 2-nitroethyl phenyl sulfide (42) which was identical in all respects to the product obtained from nitromethane (CHART C.32). 2-Nitroethyl phenyl sulfide (42) was transformed to the reagent 2-nitroethyl phenyl sulfoxide (41) in 96% yield with 4-^{t}butyl iodoxybenzene in benzene solvent at room temperature for 12 h (CHART C.33).

41: mp : $64^{\circ}C$.

ir : ν_{max} (KBr) cm^{-1}: 1570, 1380 ($-NO_2$), 1045 (SO).

nmr : δ ($CDCl_3$), 60 MHz: 3.42 (m, 2 H, $PhSOC\underline{H}_2$), 4.69 (m, 2 H, $-C\underline{H}_2NO_2$), 7.59 (s, 5 H, aromatic).

42: ir : ν_{max} (neat) cm^{-1}: 1550, 1370 ($-NO_2$).

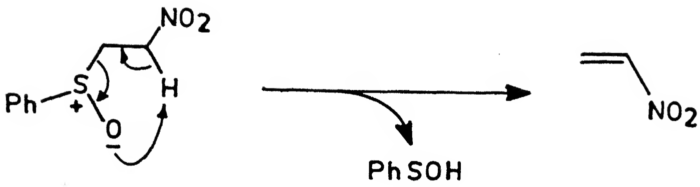
nmr : δ ($CDCl_3$), 60 MHz: 3.3 (t, 2 H, $phSC\underline{H}_2$), 4.37 (t, 2 H, $C\underline{H}_2NO_2$), 7.22 (m, 5 H, aromatic).

43: bp : $120-122^{\circ}C/0.05$ torr.

nmr : δ ($CDCl_3$), 60 MHz: 3.2-3.5 (m, 4 H, $SC\underline{H}_2C\underline{H}_2Br$), 7.21 (s, 5 H, aromatic).

The optimum conditions for the 2-bromoethyl phenyl sulfide (43) to 2-nitroethyl phenyl sulfide (42) change was determined as a result of a number of experiments involving the reagents involved in the change, the solvent and reaction conditions. In the initial stages, when compound (43) was reacted with

CHART C.31



41 40

CHART C.32

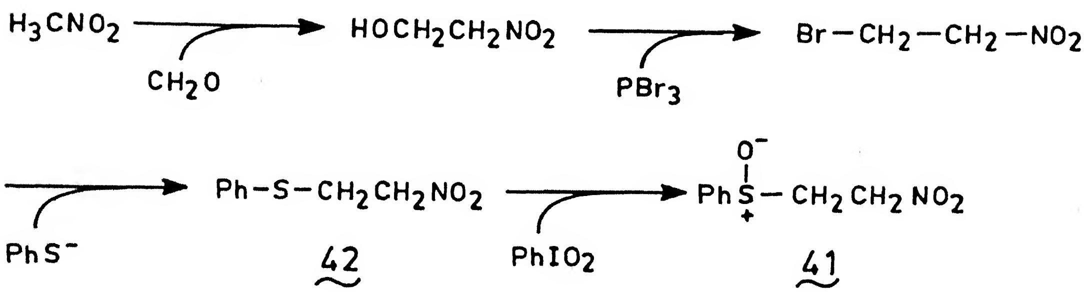
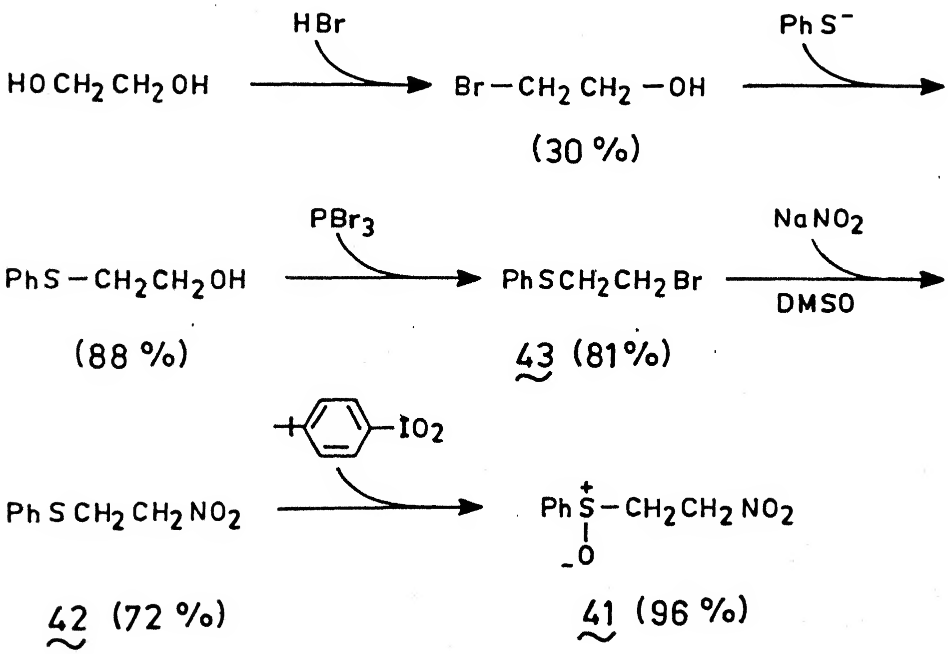
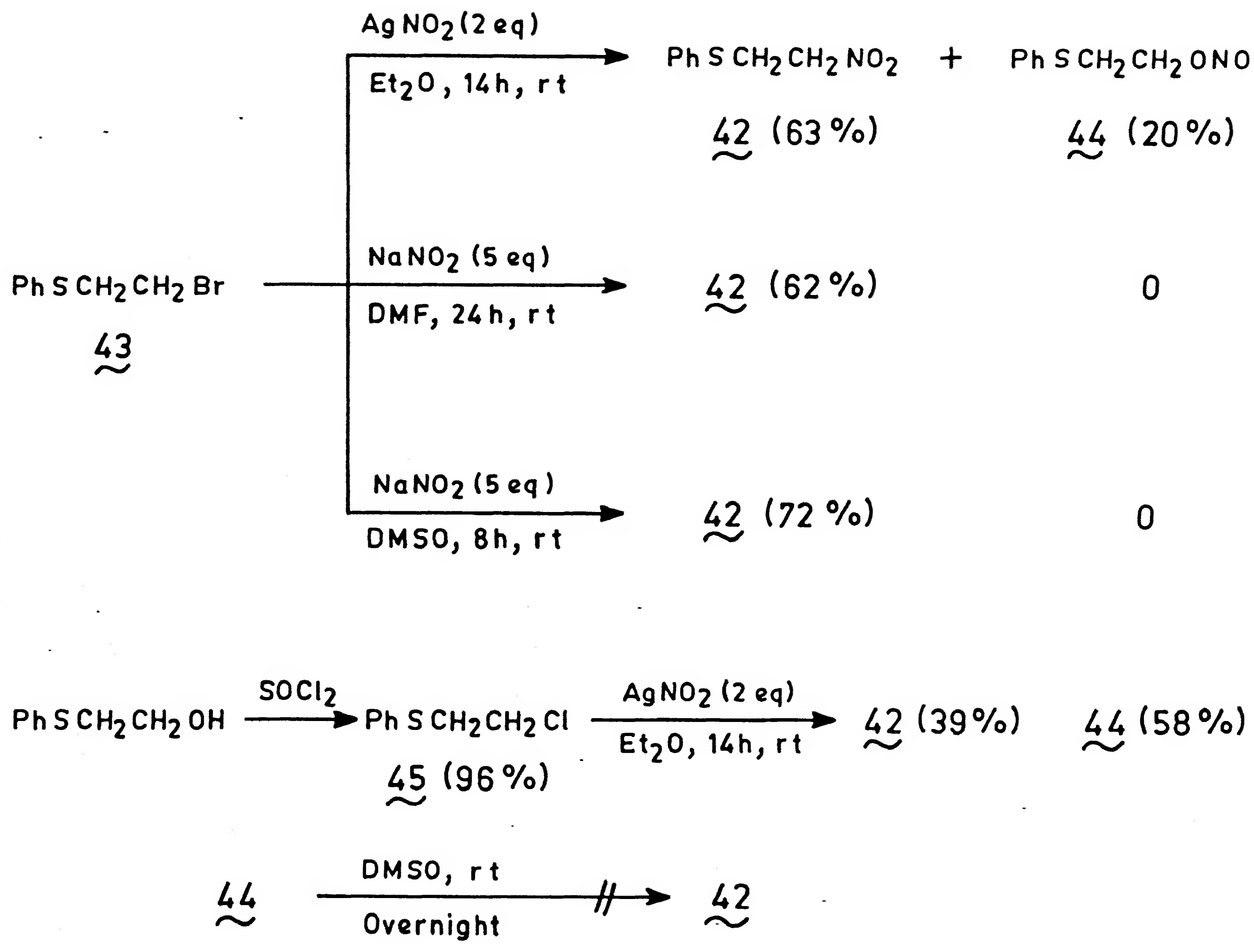


CHART C.33



2 equivalents of silver nitrite in ether at room temperature for 14 h, a 63% yield of 2-nitroethyl phenyl sulfide (42) and a 20% yield of 2-hydroxyethyl phenyl sulfidenitrite (44) was obtained thus demonstrating that under these conditions, the silver nitrite exhibits ambidient ion character in the sense both the nitro as well as nitrite are formed. In parallel experiments 2-chloroethyl phenyl sulfide (45) was prepared in 96% yields from 2-hydroxyethyl phenyl sulfide with thionyl chloride when treated with 2-equivalents of silver nitrite under conditions described above, gave a 39% yield of the nitro compound (42) and 58% yield of the nitrite (44). The reversal of preference with respect to formation of the nitro and the nitrite compounds exhibited by (43) and (45) show the importance of the leaving group, relating to the fate of the overall reaction. 2-Bromoethyl phenyl sulfide (43) when treated with 5-equivalents of sodium nitrite in DMF for 24 h at room temperature gave a 62% yield of the nitro compound and none of the nitrite. As described earlier, when DMSO was used as solvent, the product 42 could be obtained, without any formation of the undesired nitrite in 72% yields, at a reduced time span of 8 h at room temperature. Finally, it was established that the nucleophilic attack on the substrate determines the overall product composition in the sense that the nitrite does not rearrange to the nitro compound under the reaction conditions (CHART C.34).

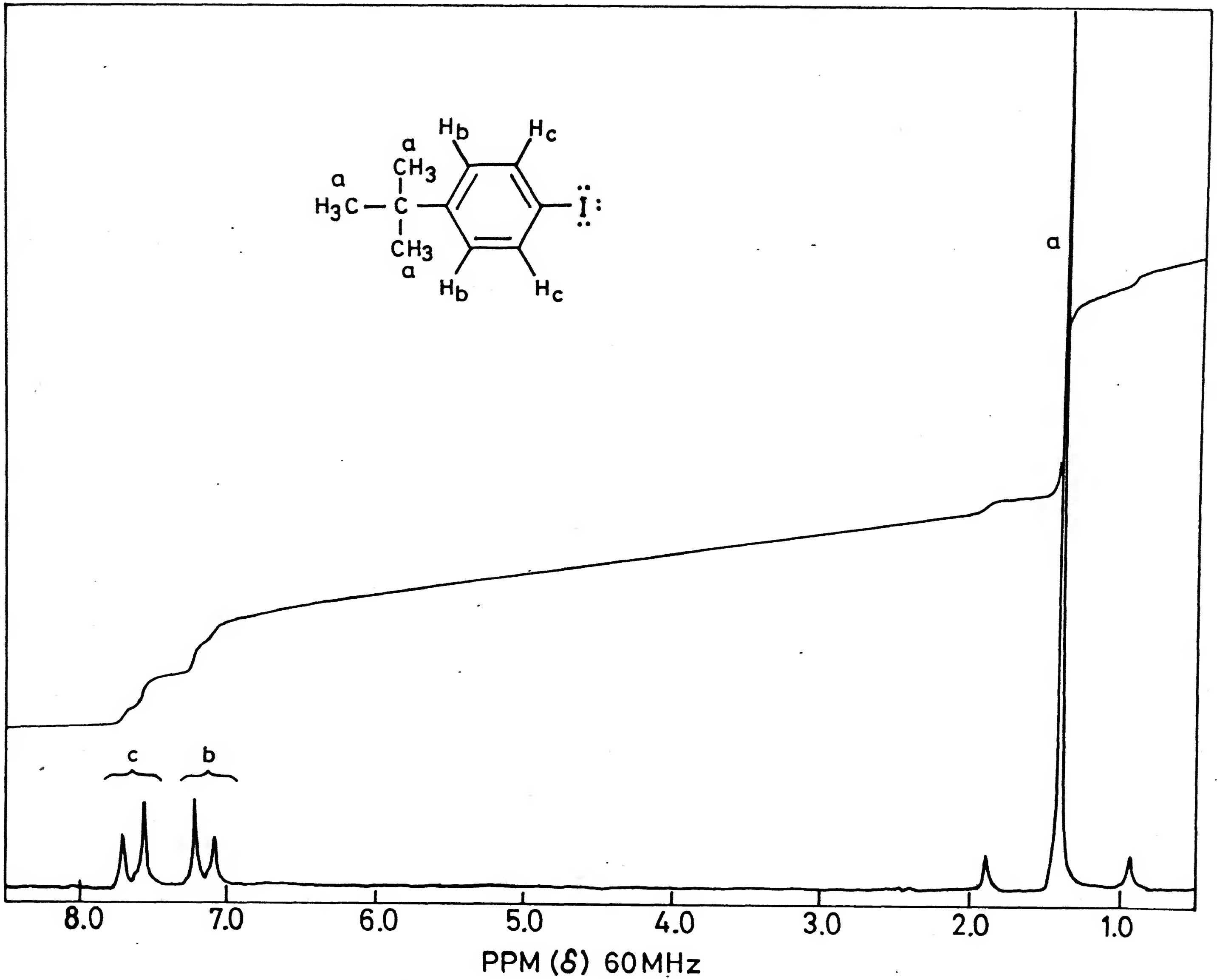
CHART C.34



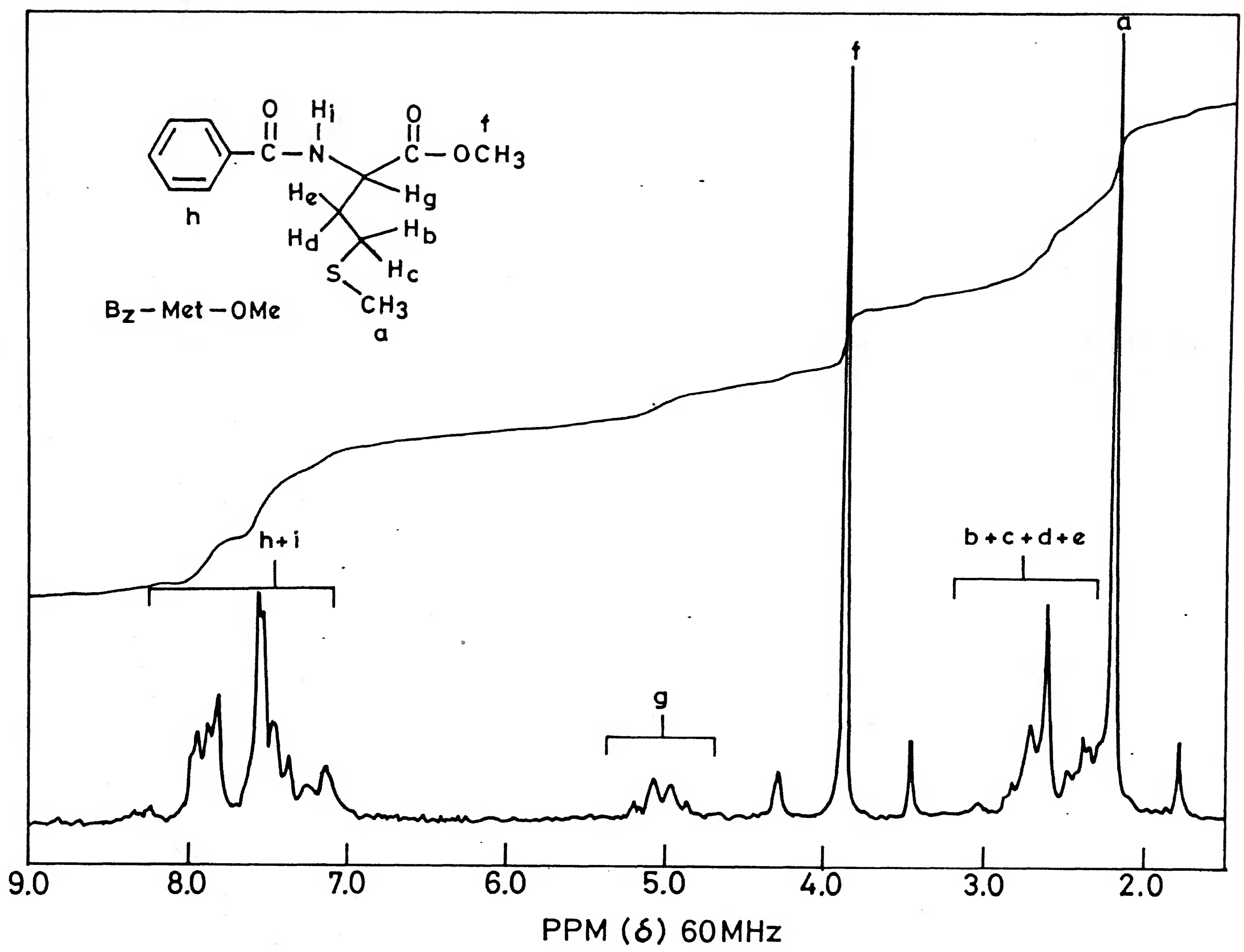
Ph S CH2 CH2 Br
43
Ag NO2 (2 eq)
Et2O, 14h, rt
Na NO2 (5 eq)
DMF, 24h, rt
Na NO2 (5 eq)
DMSO, 8h, rt
Ph S CH2 CH2 NO2
+
Ph S CH2 CH2 ONO
42 (63 %)
44 (20 %)
42 (62 %)
0
42 (72 %)
0
Ph S CH2 CH2 OH
SOCl2
Ph S CH2 CH2 Cl
45 (96 %)
Ag NO2 (2 eq)
Et2O, 14h, rt
42 (39 %)
44 (58 %)
44
DMSO, rt
Overnight
42

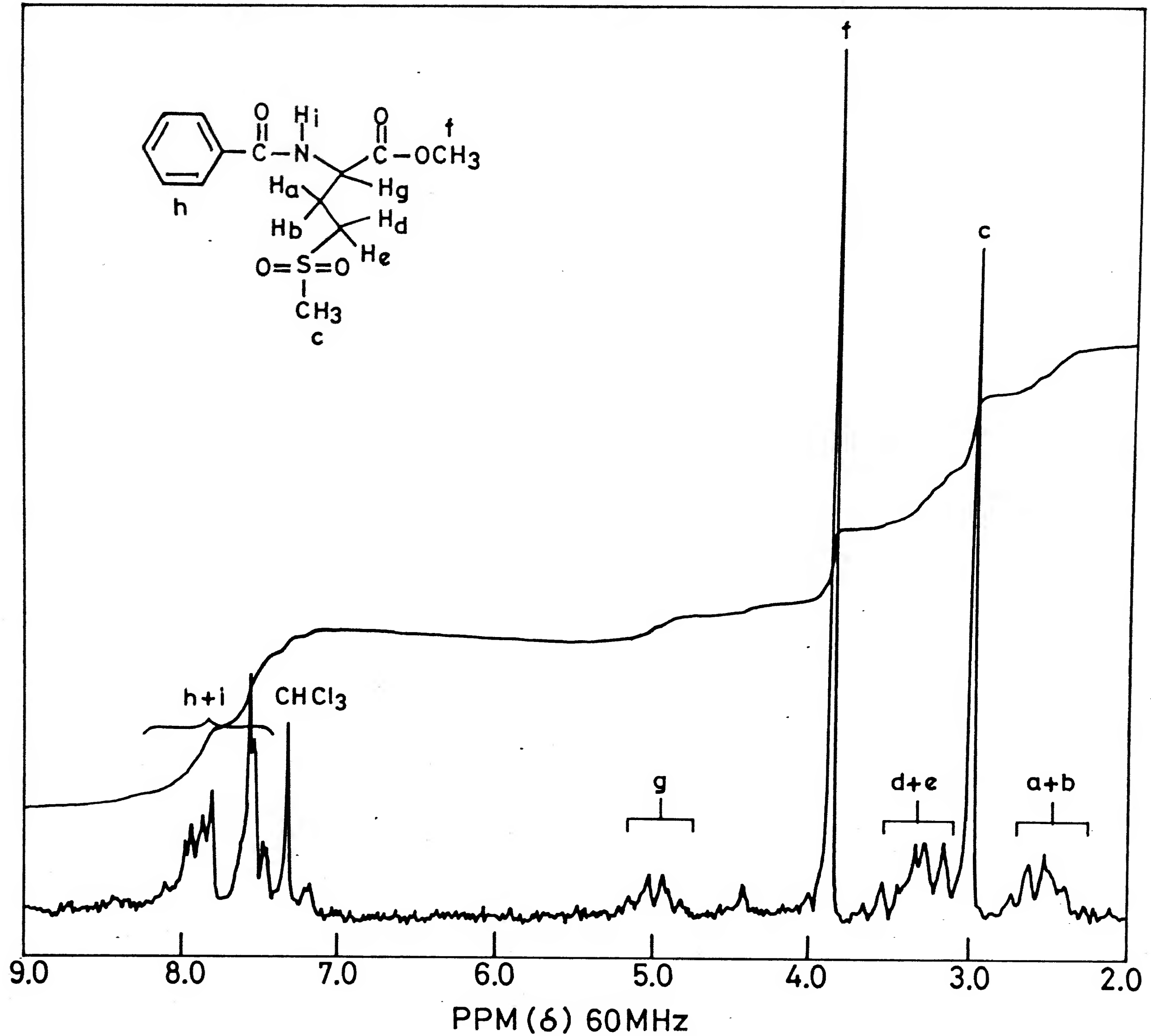
44:	ir	:	ν_{max} (neat) cm^{-1}: 1640, 1280 (ON=O).
	nmr	:	δ ($CDCl_3$), 60 MHz: 3.06 (t, 2 H, pHSC$\underline{H}_2$), 4.45 (t, 2 H, C$\underline{H}_2$ON=O), 7.25 (s, 5 H, aromatic).
45:	bp	:	114°C/2 torr.
	nmr	:	δ ($CDCl_3$), 60 MHz: 2.9-3.22 (m, 2 H, SC$\underline{H}_2$), 3.4-3.7 (m, 2 H, C$\underline{H}_2$Cl), 7.2 (s, 5 H, aromatic),

Since 2-nitroethyl phenyl sulfoxide (41) has been already demonstrated to fragment readily and quantitatively to nitroethylene on benzene reflux, the exceptionally facile route described for this compound from very easily available starting materials and obviating hazardous chemicals and procedures should further encourage the use of nitroethylene in organic synthesis.

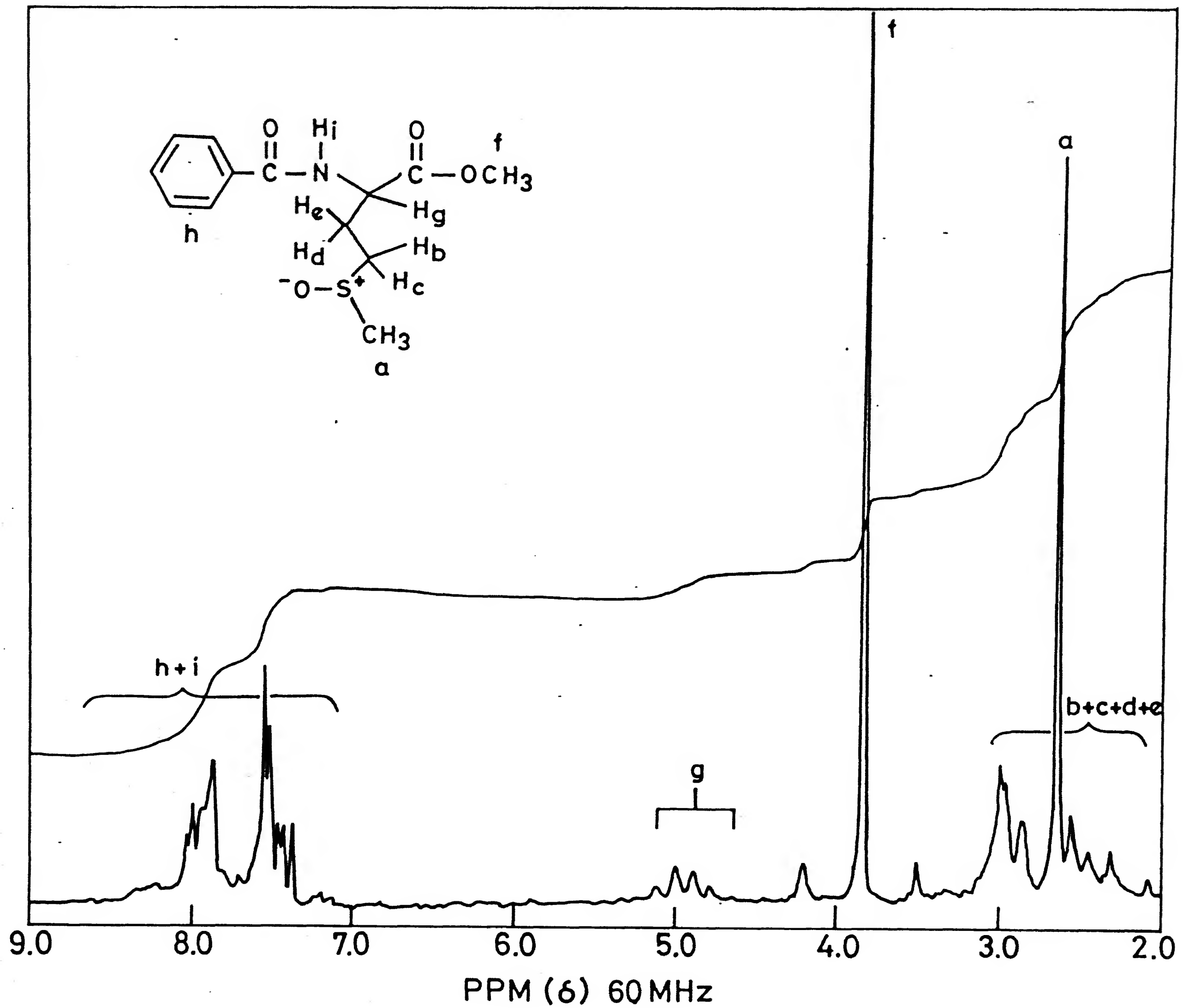


a
CH3
a
H3C
C
CH3
a
Hb
Hc
Hb
Hc
I
a
c
b
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60MHz

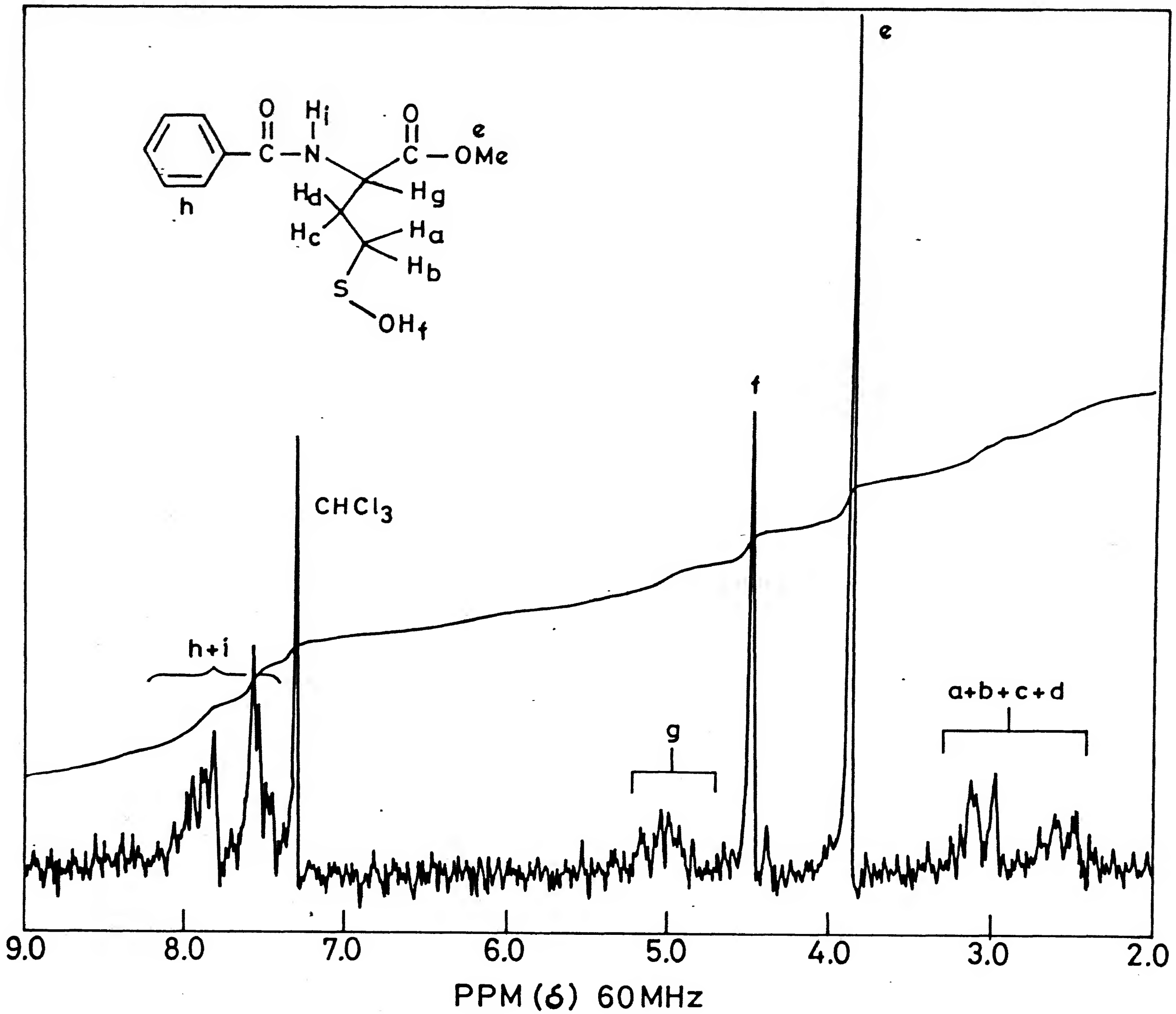

h
Hi
f
OCH3
He
Hg
Hd
Hb
Hc
S
CH3
a
Bz - Met - OMe
f
a
h+i
b+c+d+e
g
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz

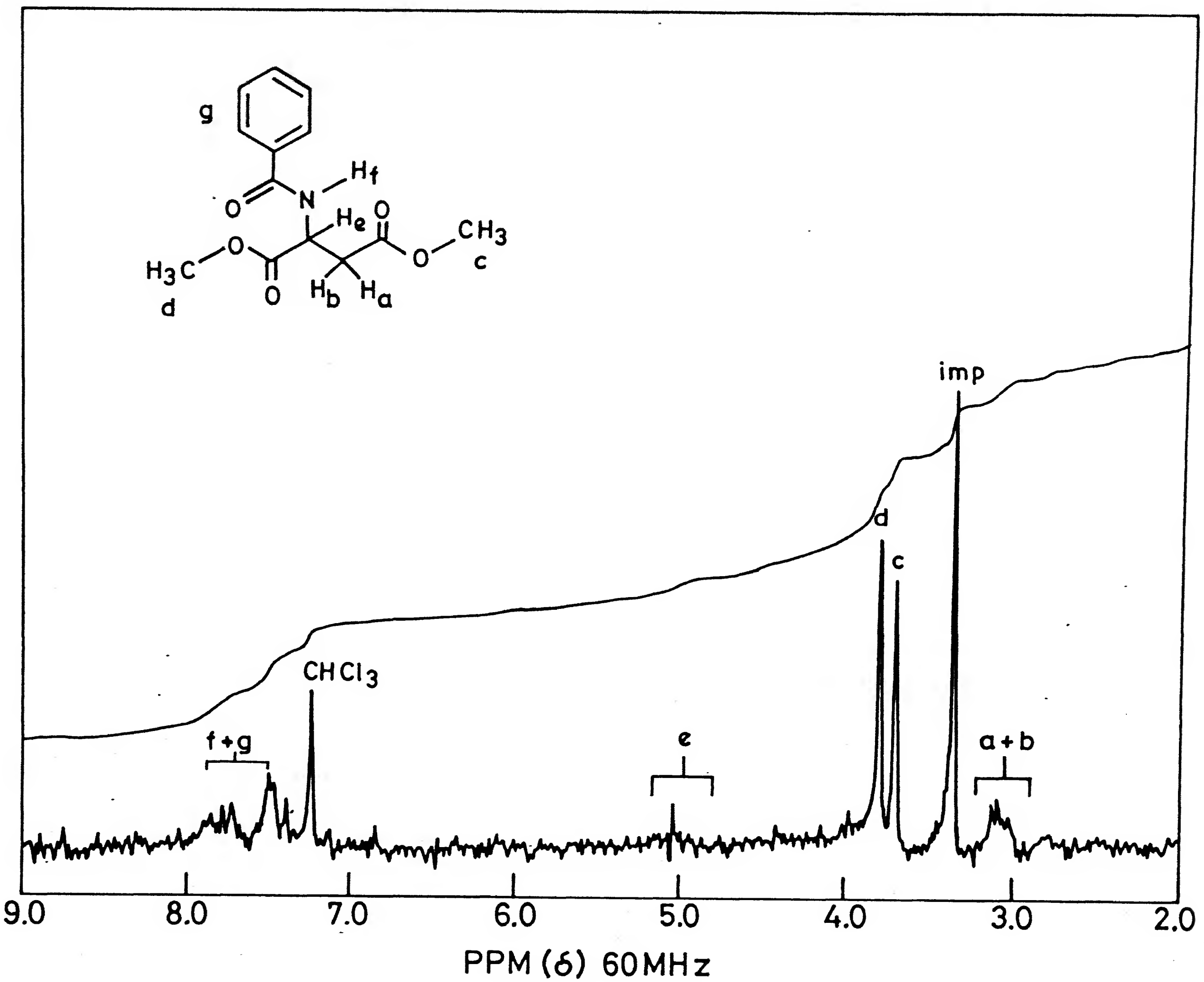


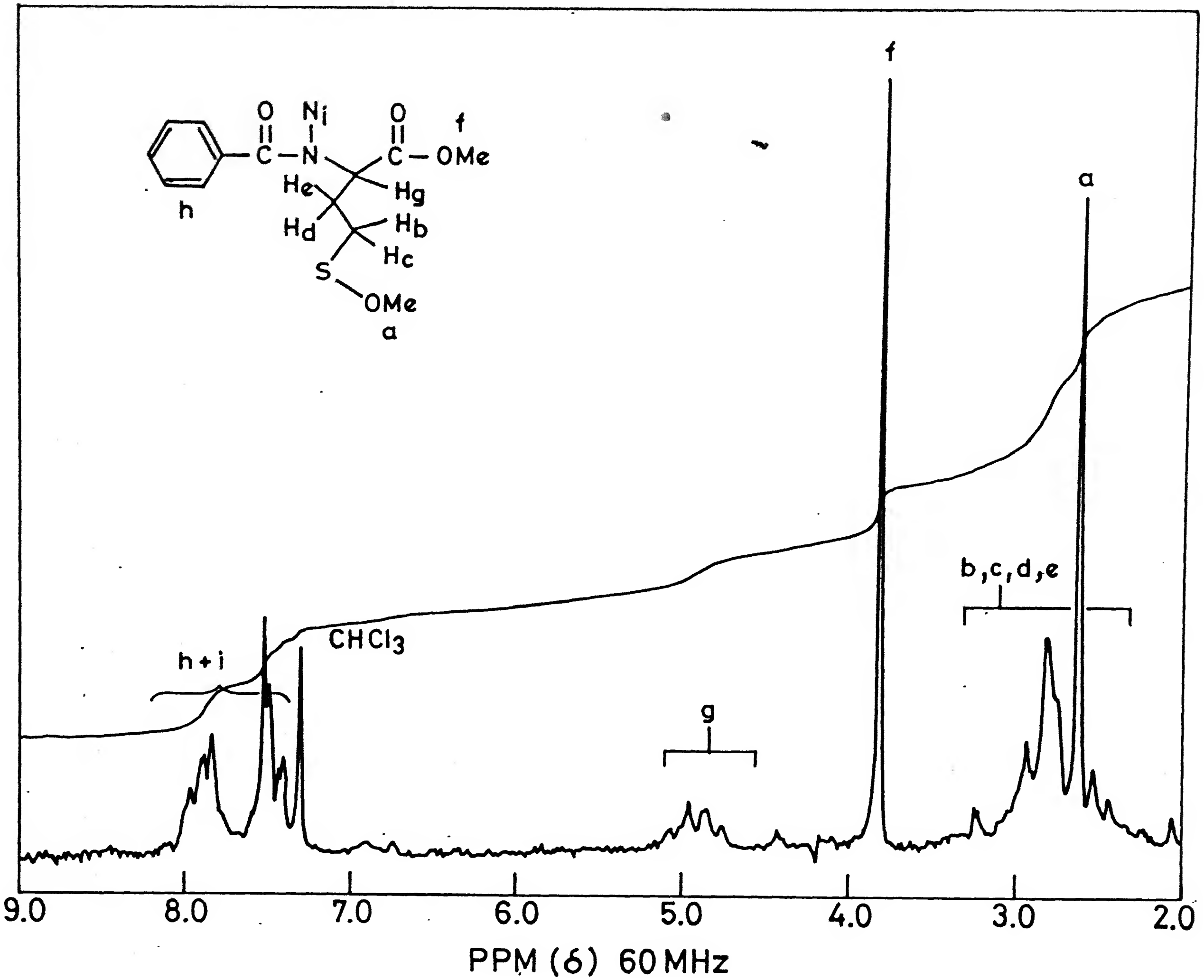
h
O
Hi
O
f
C—N
C—OCH3
Ha
Hg
Hb
Hd
He
O=S=O
CH3
c
f
c
h+i
CHCl3
g
d+e
a+b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz



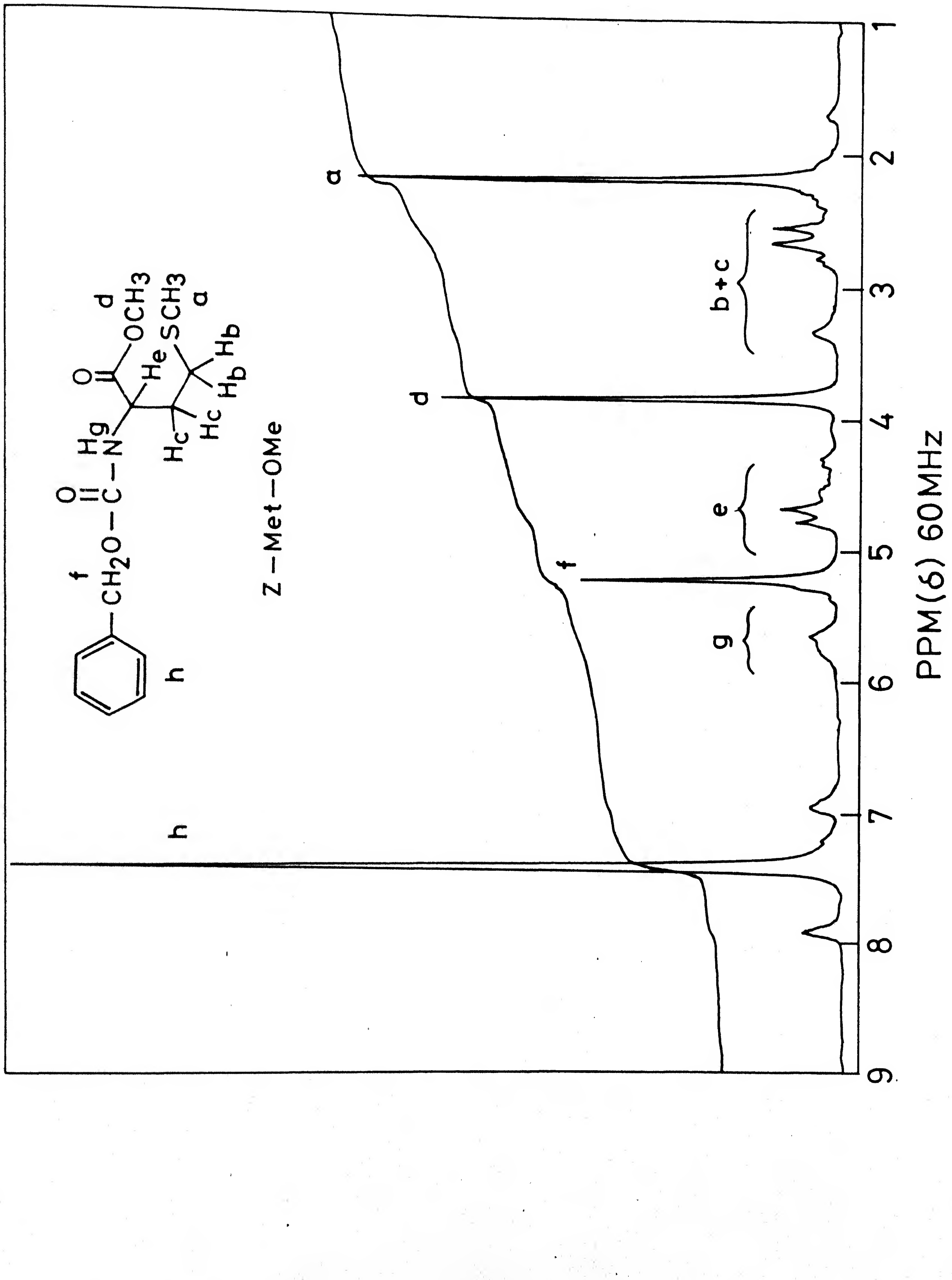
h
Hi
f
OCH3
He
Hg
Hd
Hb
Hc
-O-S+
CH3
a
f
a
h+i
g
b+c+d+e
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz

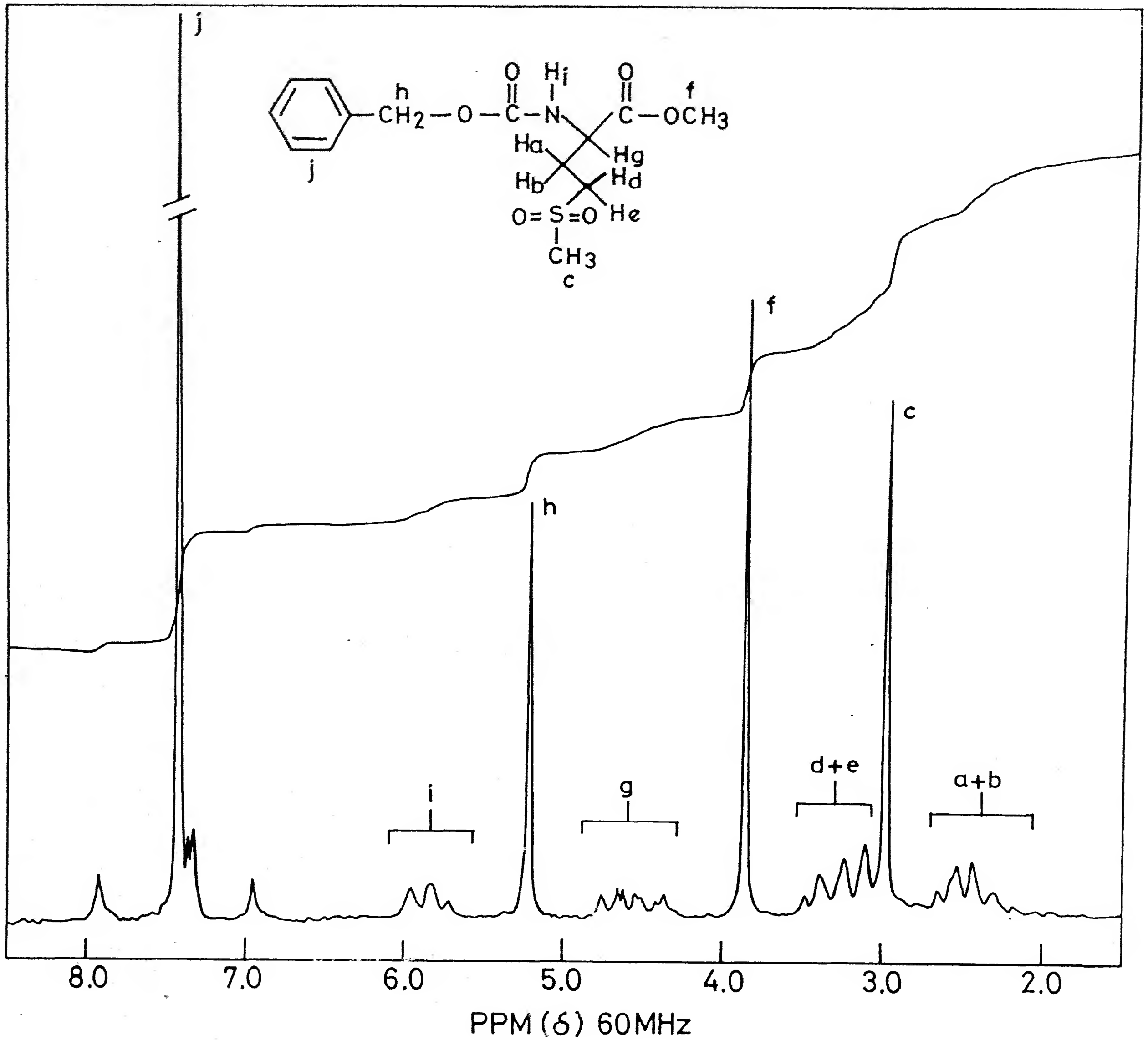

h
Hi
e
OMe
Hg
Hd
Hc
Ha
Hb
S
OHf
e
f
CHCl3
h+i
g
a+b+c+d
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz

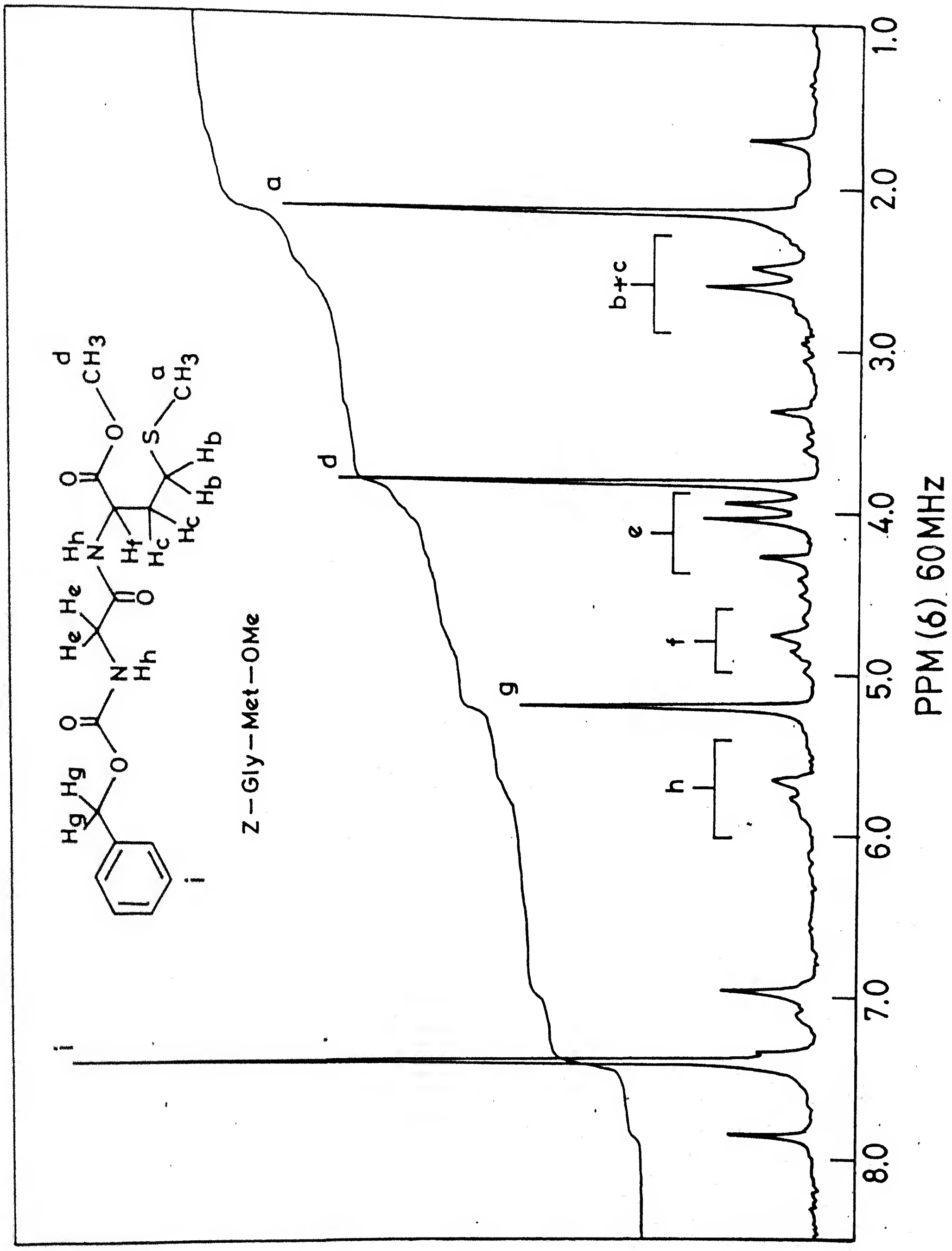

g
H_f
H_e
H_a
H_b
H_3C
d
CH_3
c
imp
d
c
$CHCl_3$
f+g
e
a+b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz



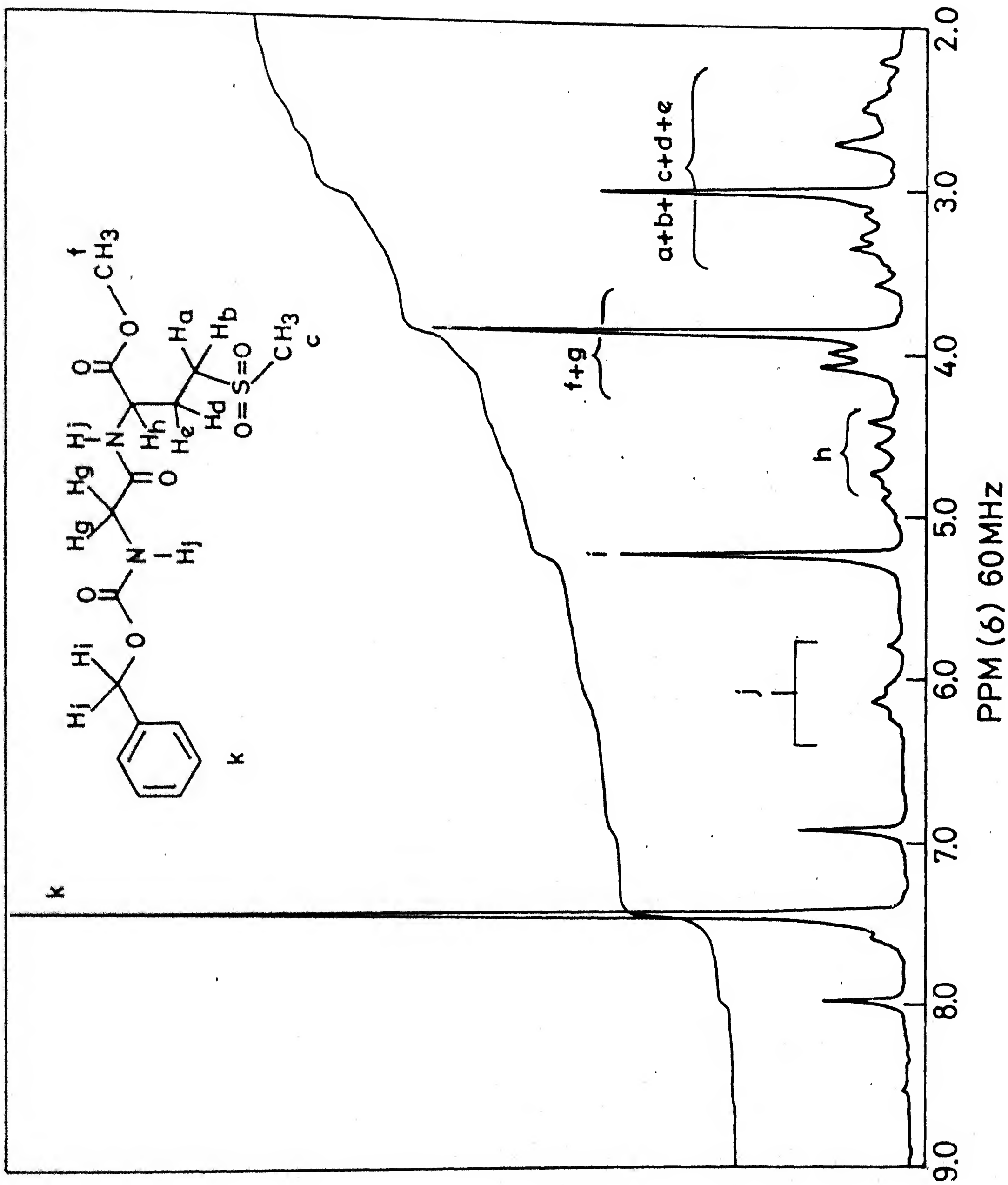
h
Ni
f
OMe
He
Hg
Hd
Hb
Hc
S
OMe
a
f
a
b,c,d,e
h+i
CHCl3
g
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60 MHz


Z—Met—OMe
PPM(δ) 60MHz
h
f
e
d
b+c
a
g
1
2
3
4
5
6
7
8
9

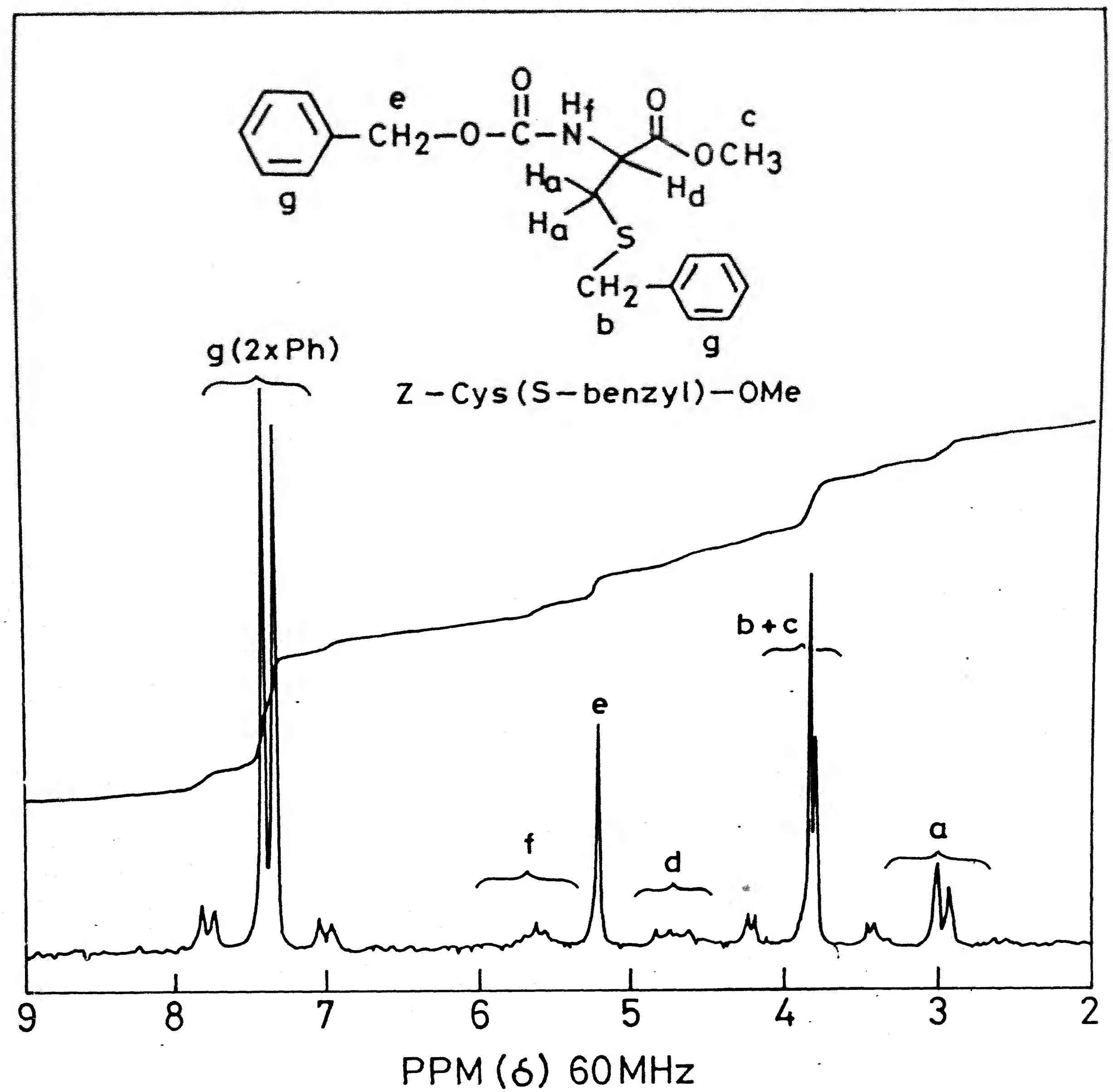

j
h
f
c
i
g
d+e
a+b
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz

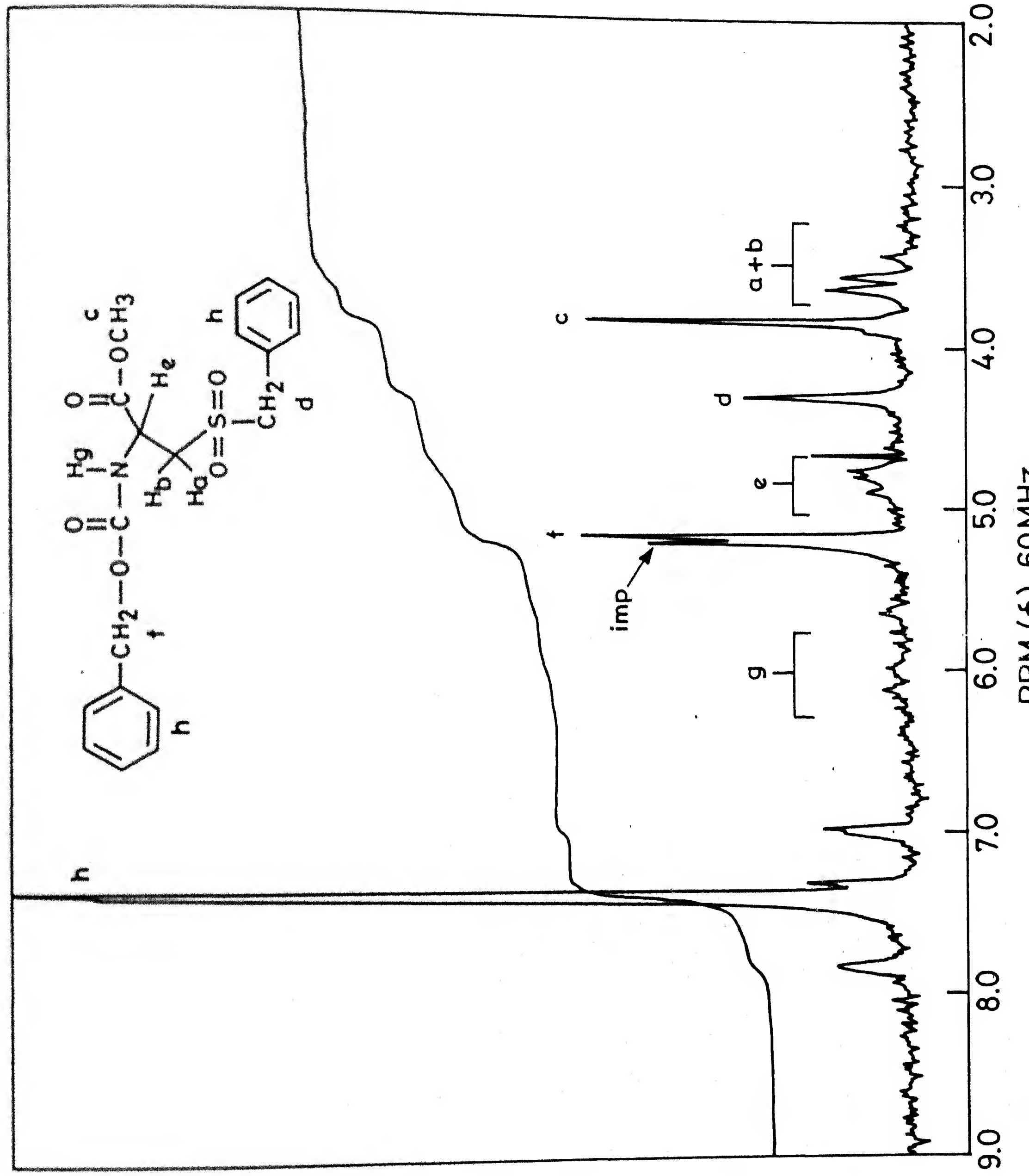


Z–Gly–Met–OMe
a
b+c
d
e
f
g
h
i
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
PPM (δ) 60 MHz

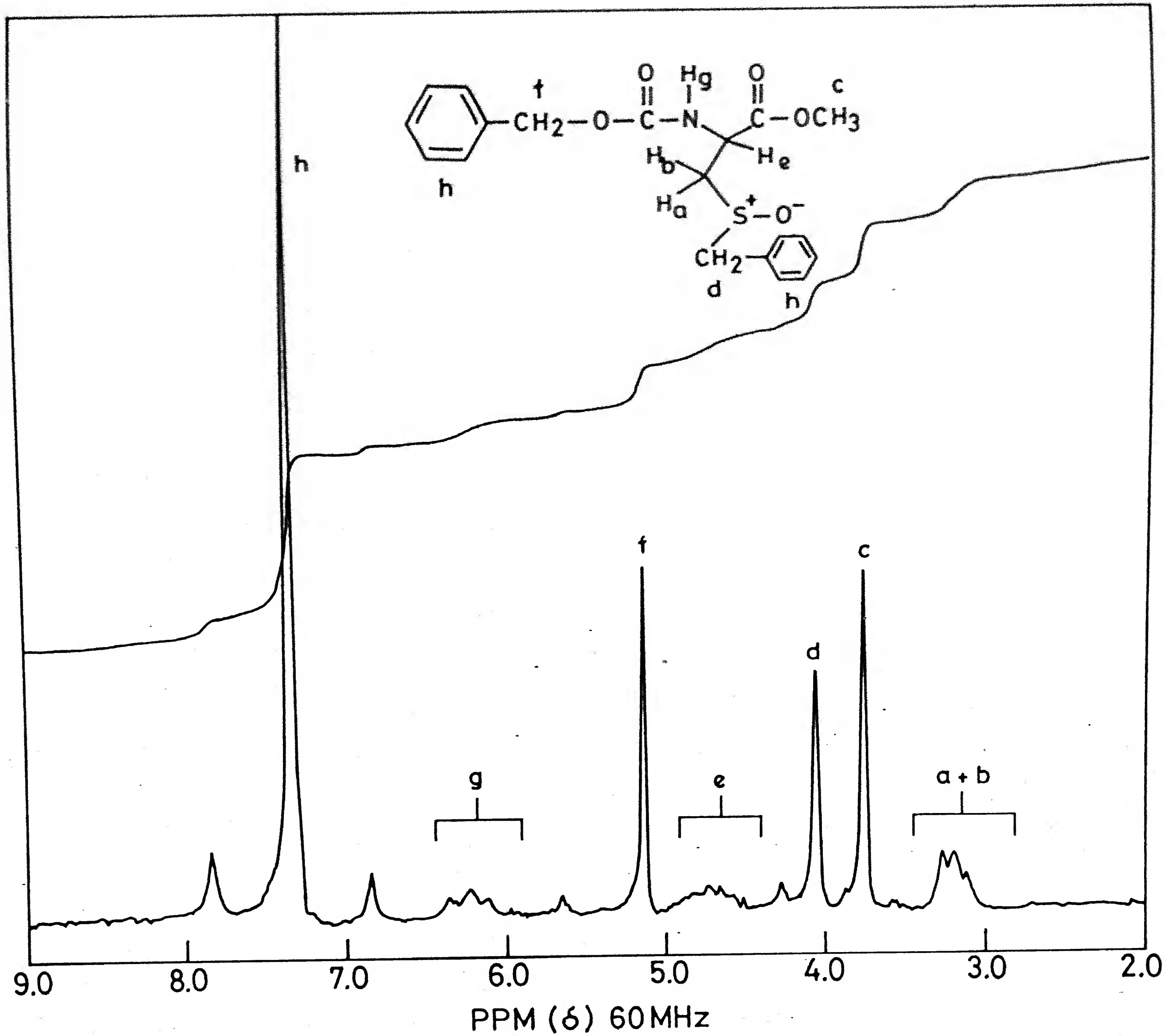


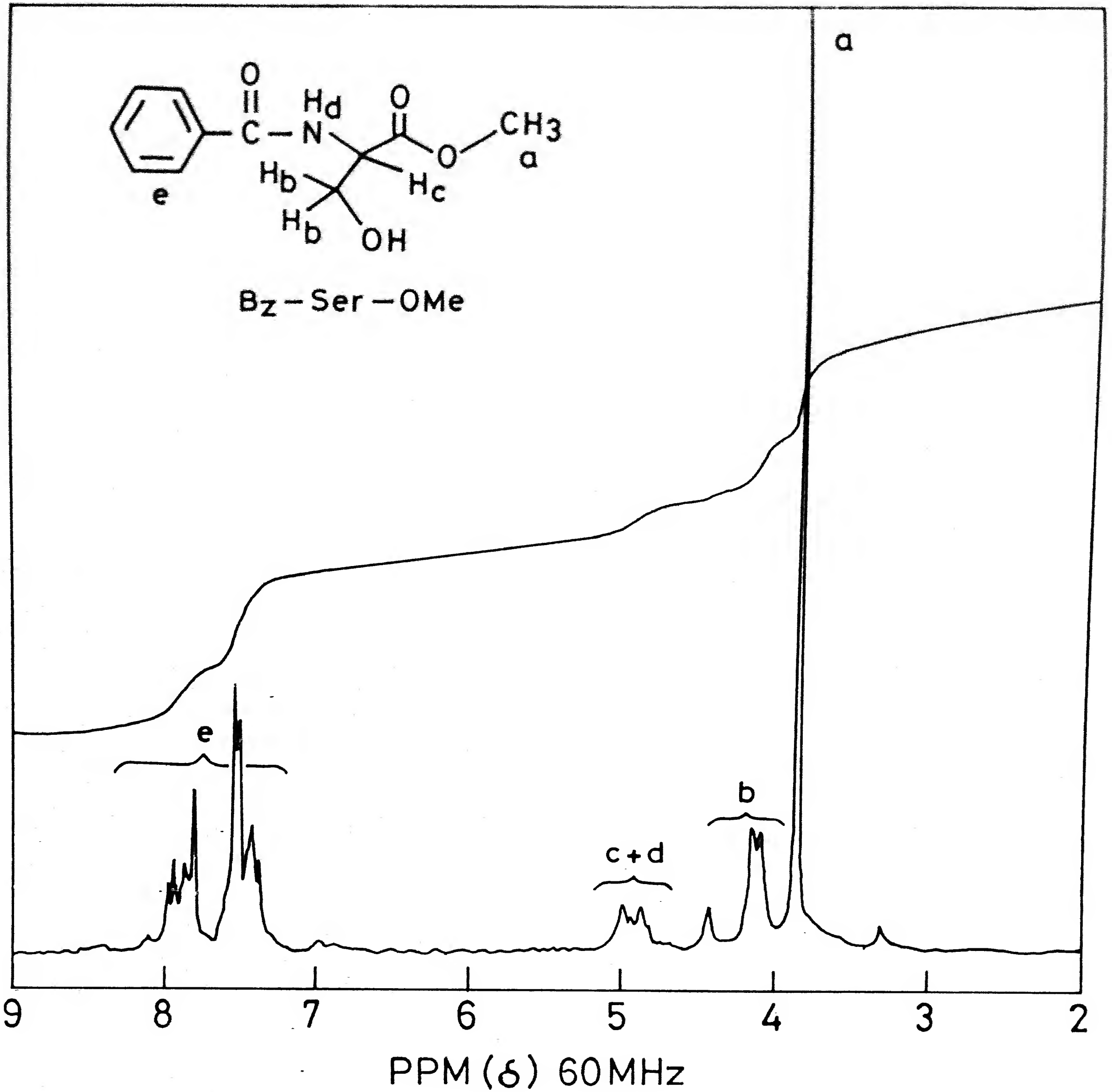
PPM (δ) 60MHz
a+b+c+d+e
f+g
h
i
j
k

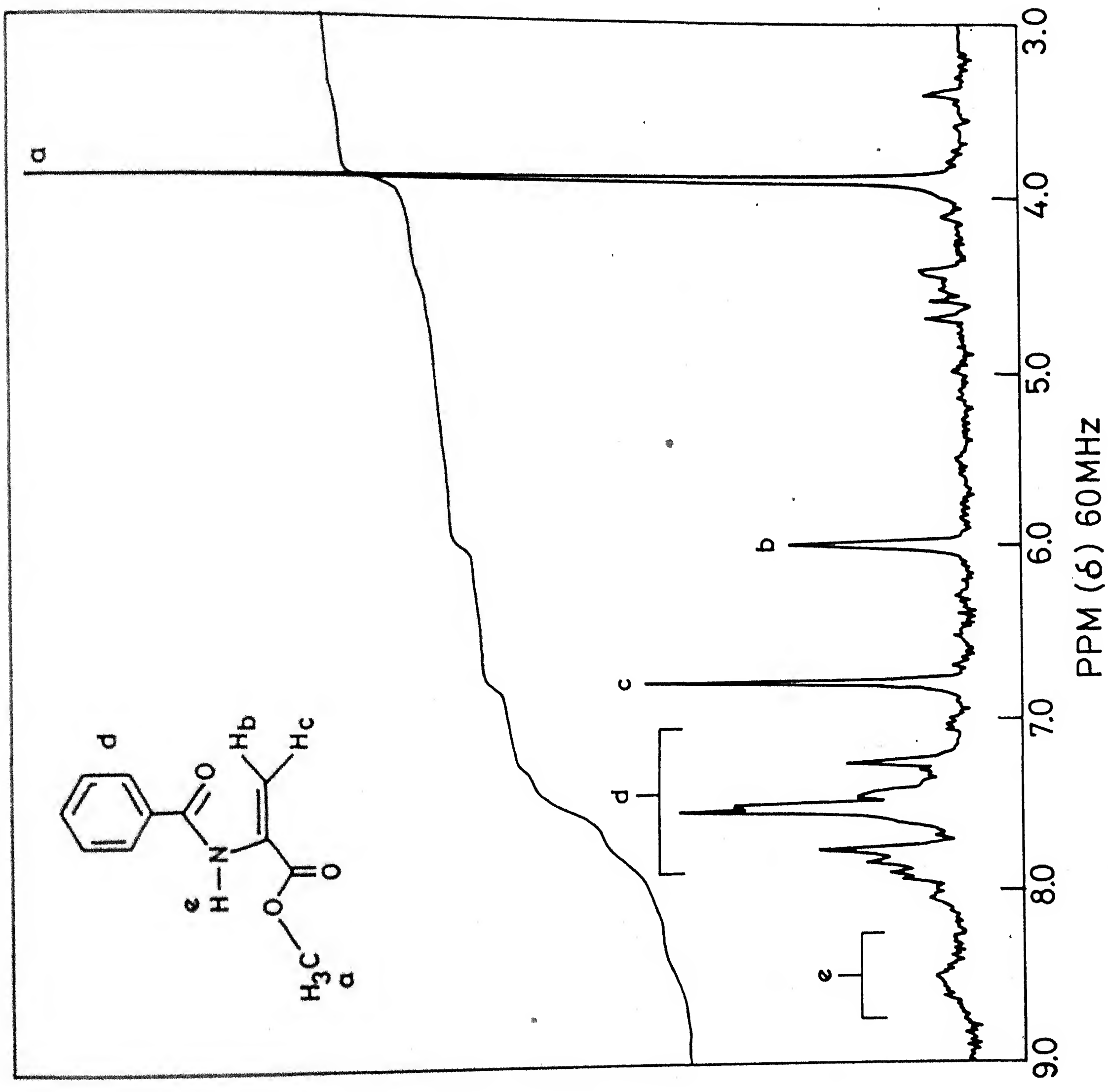

Z – Cys (S – benzyl) – OMe
g (2x Ph)
f
e
d
b + c
a
9 8 7 6 5 4 3 2
PPM (δ) 60MHz



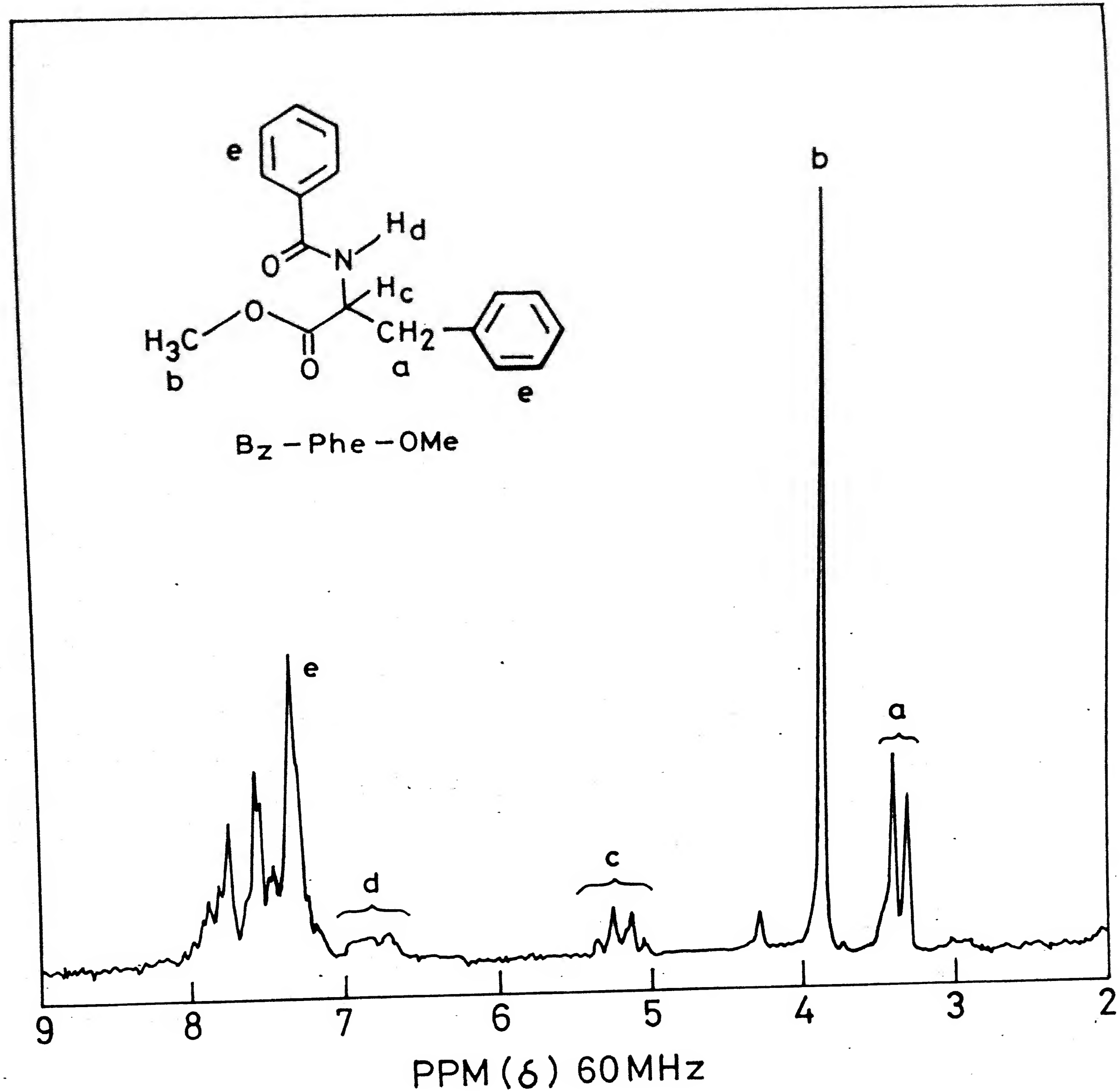
PPM (δ) 60MHz
imp
a+b
c
d
e
f
g
h
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0

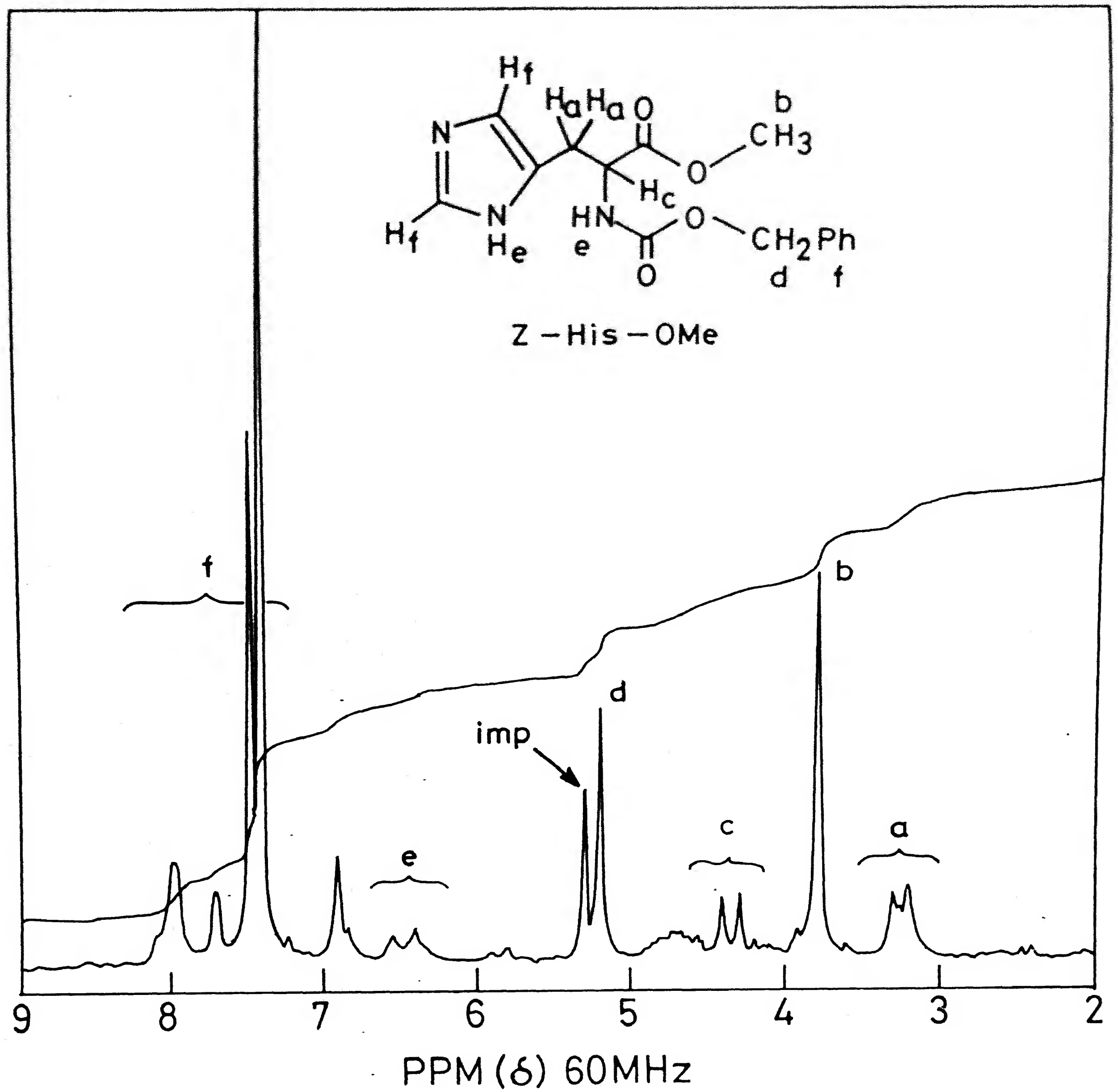

t
O
Hg
O
c
CH2—O—C—N—C—OCH3
He
Hb
Ha
S—O
CH2
d
h
h
h
f
c
d
g
e
a + b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz


Bz—Ser—OMe
a
b
c+d
e
9
8
7
6
5
4
3
2
PPM (δ) 60MHz

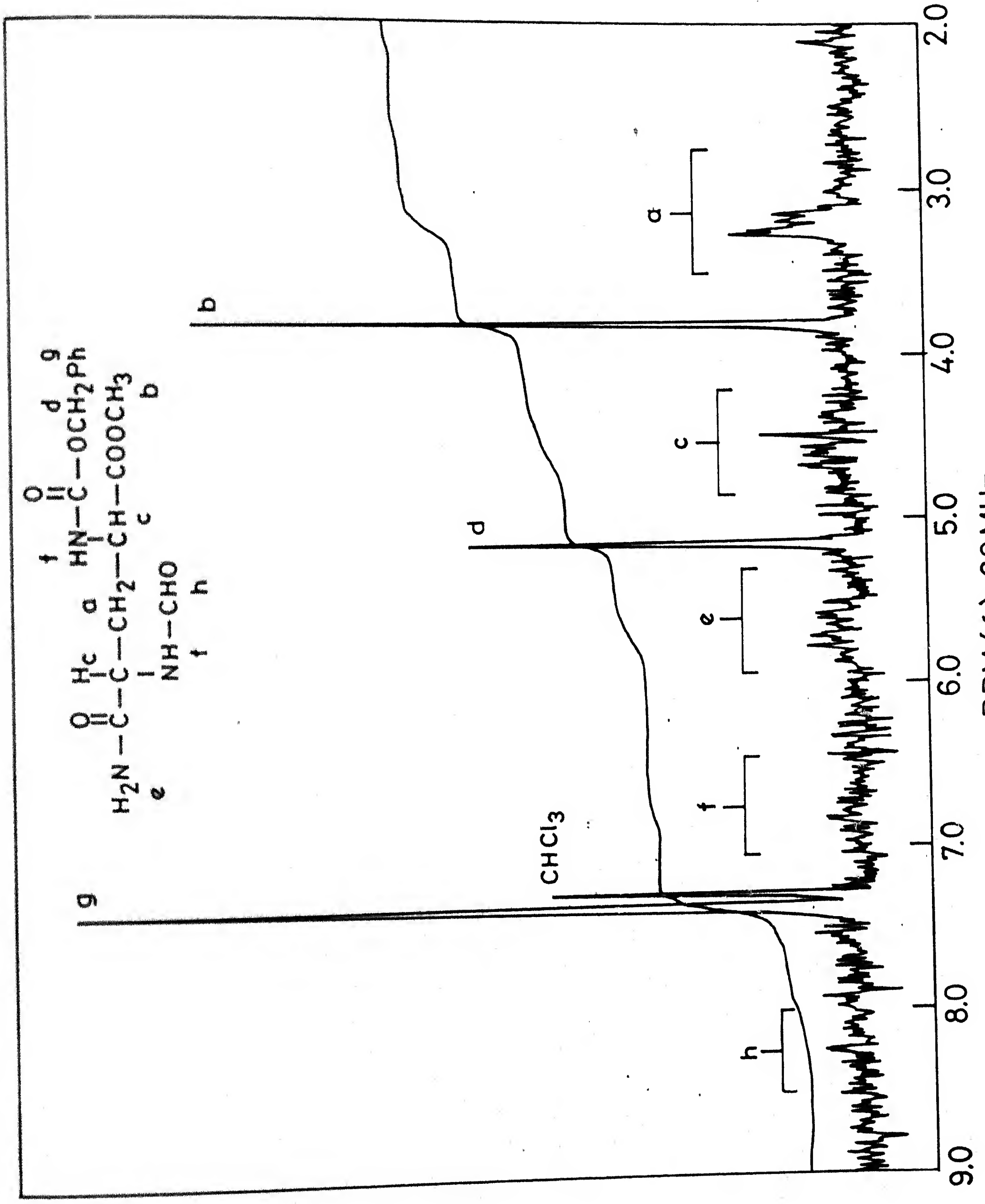


PPM (δ) 60MHz
3.0
4.0
5.0
6.0
7.0
8.0
9.0
a
b
c
d
e
H_3C
H—N
O
Hb
Hc


e
H_d
N
O
H_c
H_3C
O
CH_2
O
b
a
e
Bz – Phe – OMe
b
e
a
d
c
9
8
7
6
5
4
3
2
PPM (δ) 60MHz



Z-His-OMe
imp
a
b
c
d
e
f
9
8
7
6
5
4
3
2
PPM (δ) 60MHz



$H_2N-\overset{O}{\overset{\|}{C}}-\underset{NH-CHO}{\overset{H_c}{C}}-CH_2-\underset{c}{CH}-\overset{\overset{O}{\|}}{\underset{HN-C-OCH_2Ph}{}}$

H_2N e, a, c, f, h, f, d, g

$HN-C-OCH_2Ph$

$COOCH_3$ b

$NH-CHO$

g

CHCl$_3$

d

b

h

f

e

c

a

9.0

8.0

7.0

6.0

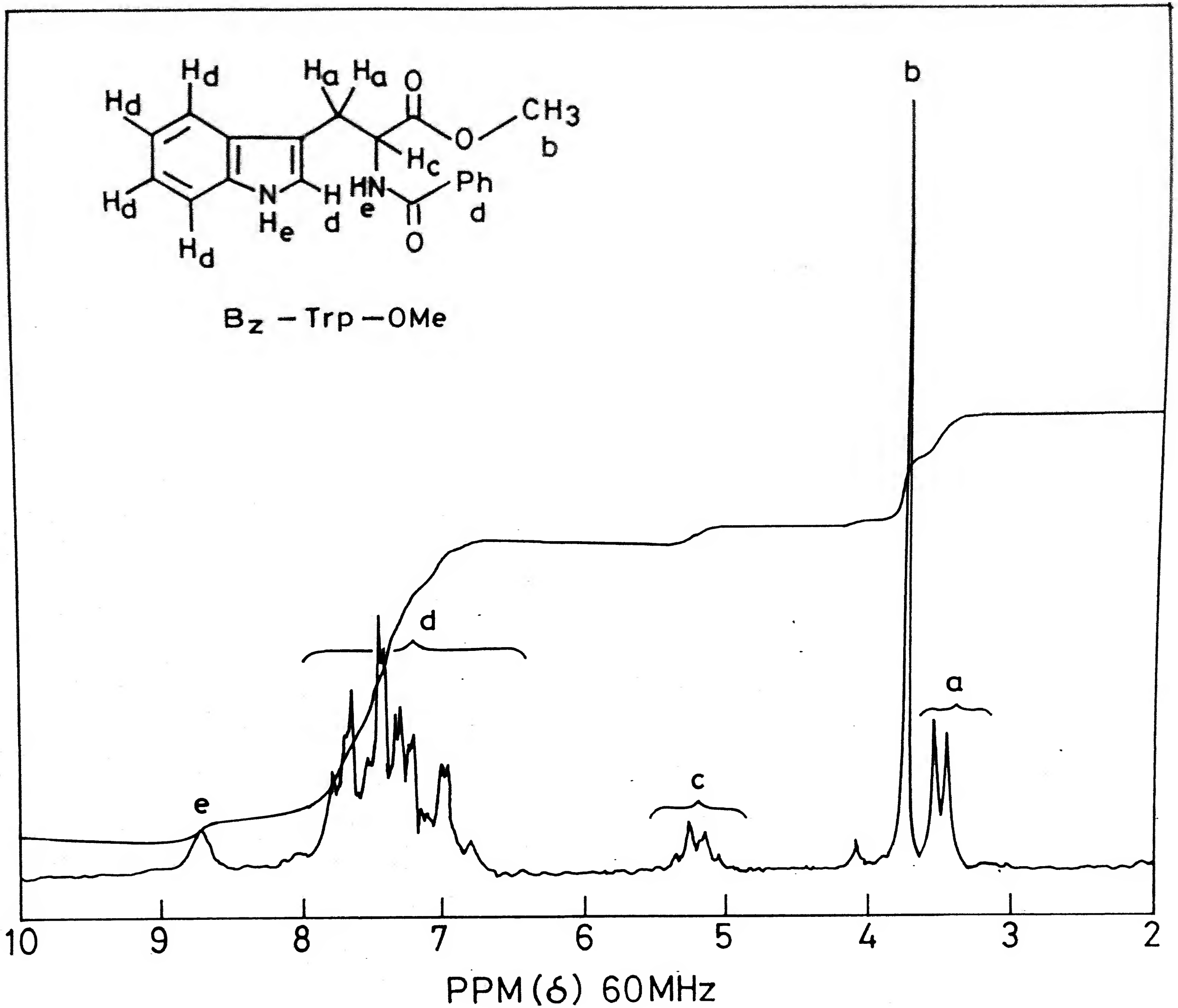
5.0

4.0

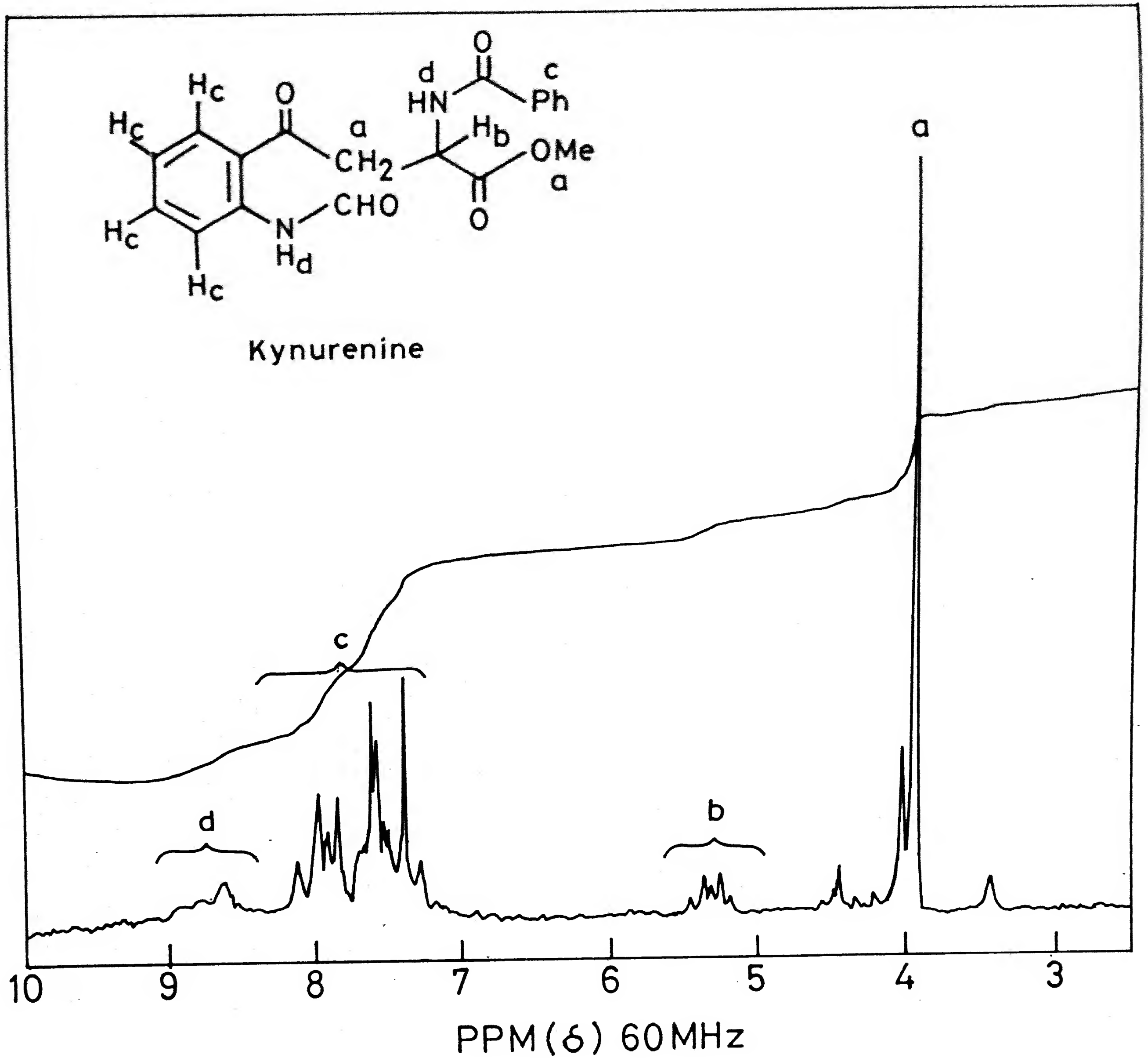
3.0

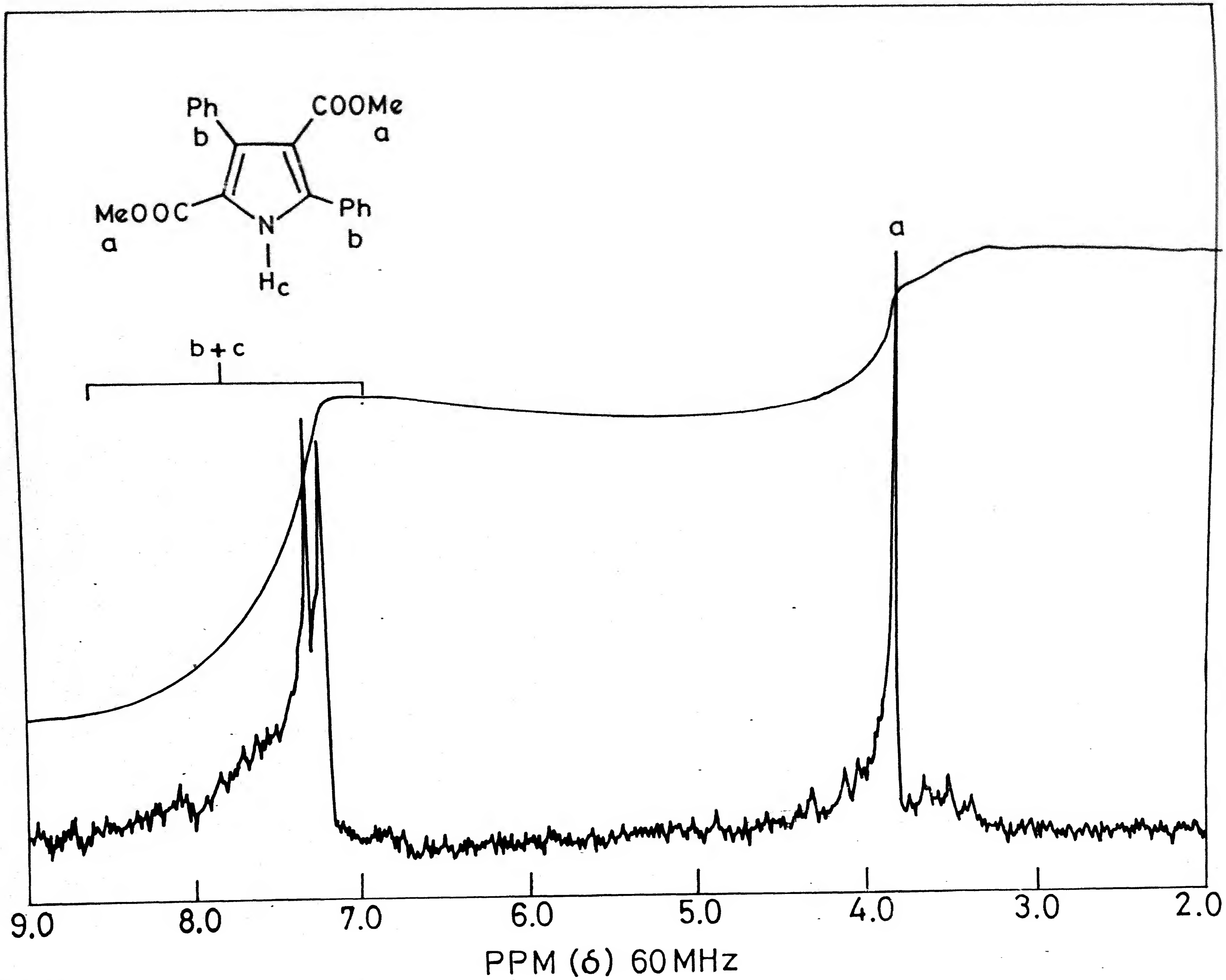
2.0

PPM (δ) 60MHz

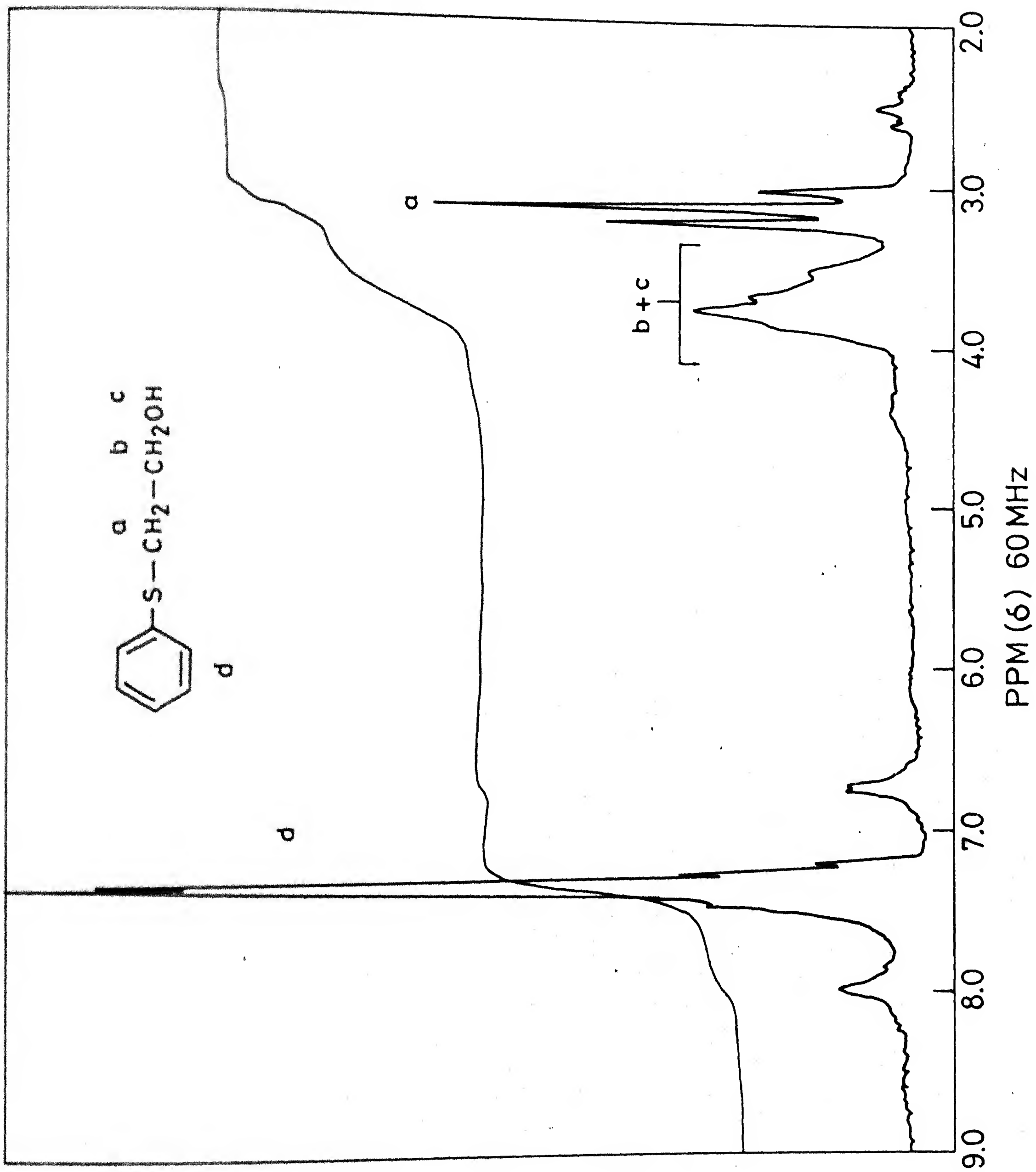


Bz — Trp — OMe
b
a
c
d
e
10
9
8
7
6
5
4
3
2
PPM (δ) 60MHz

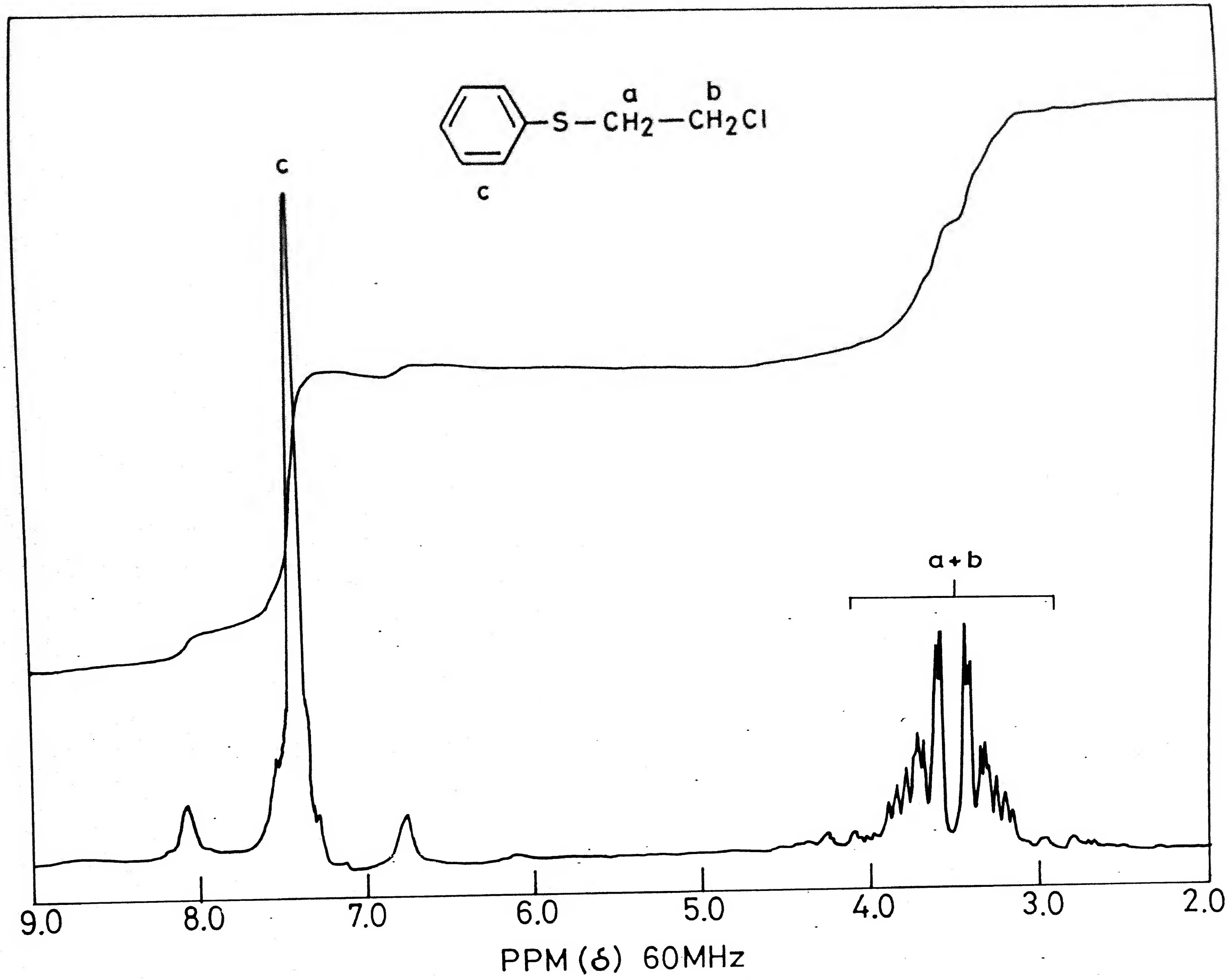

Kynurenine
a
b
c
d
10
9
8
7
6
5
4
3
PPM(δ) 60MHz



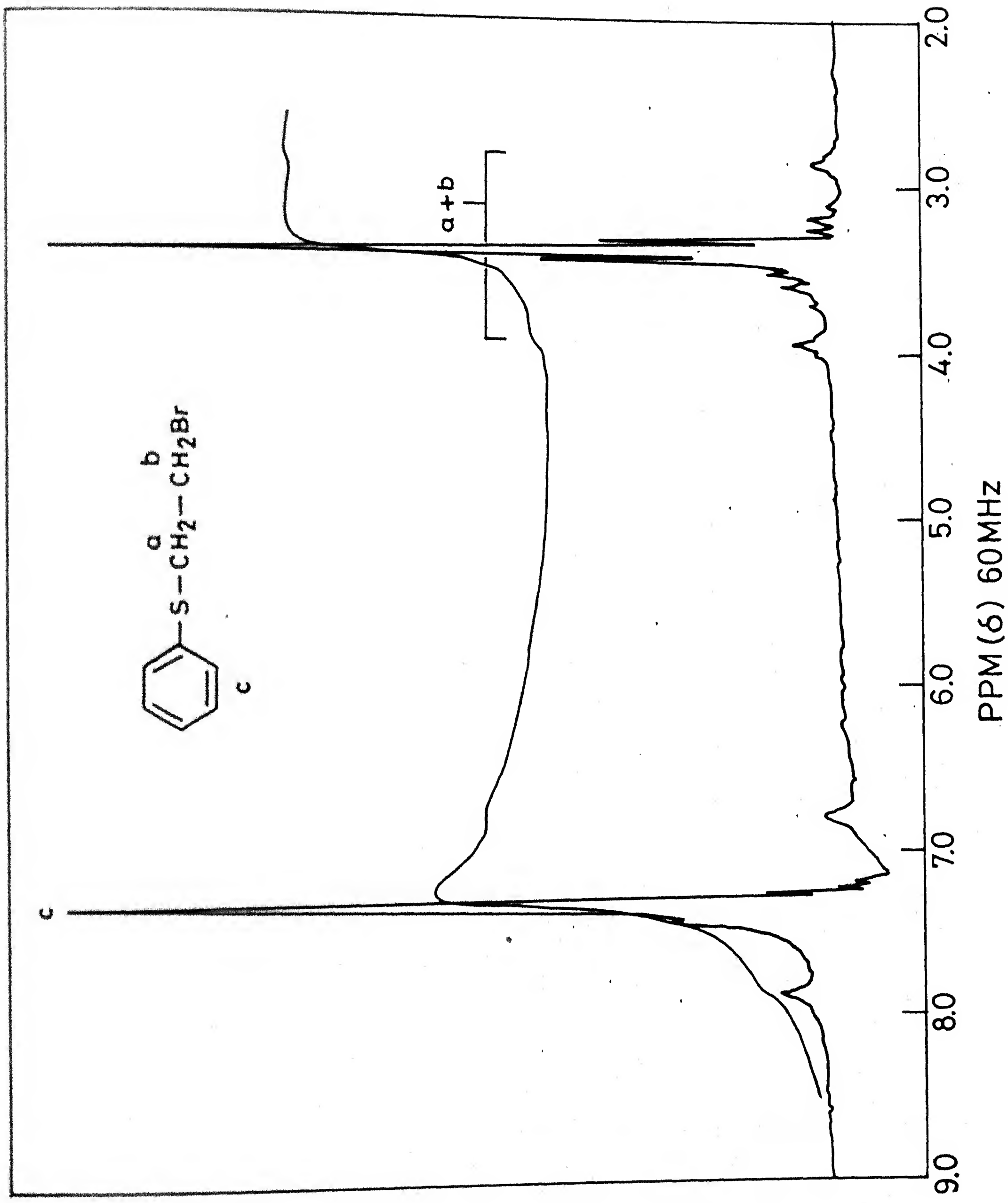
Ph
b
COOMe
a
MeOOC
a
N
Ph
b
Hc
b + c
a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz



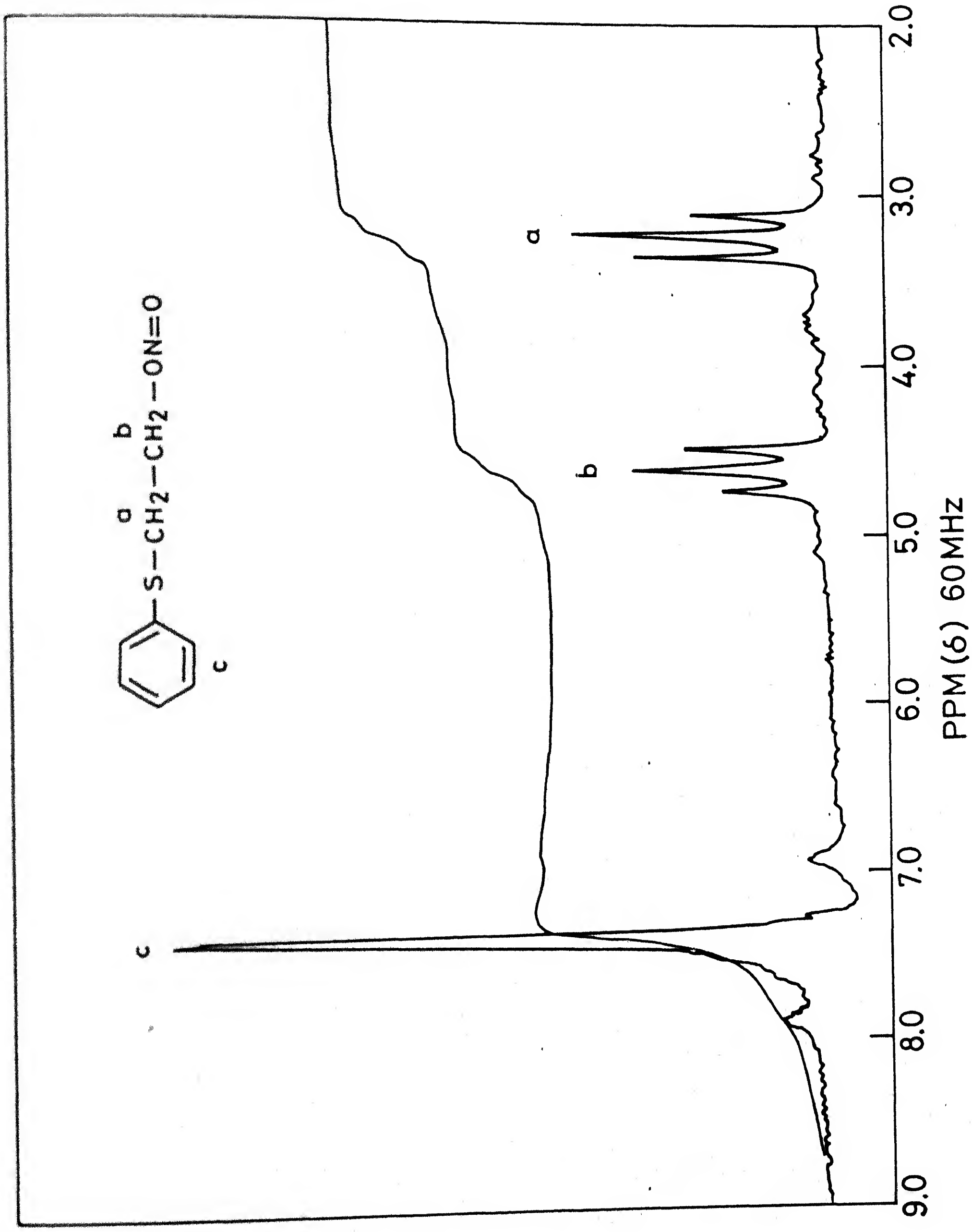
a b c
S—CH2—CH2OH
d
d
a
b + c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60 MHz

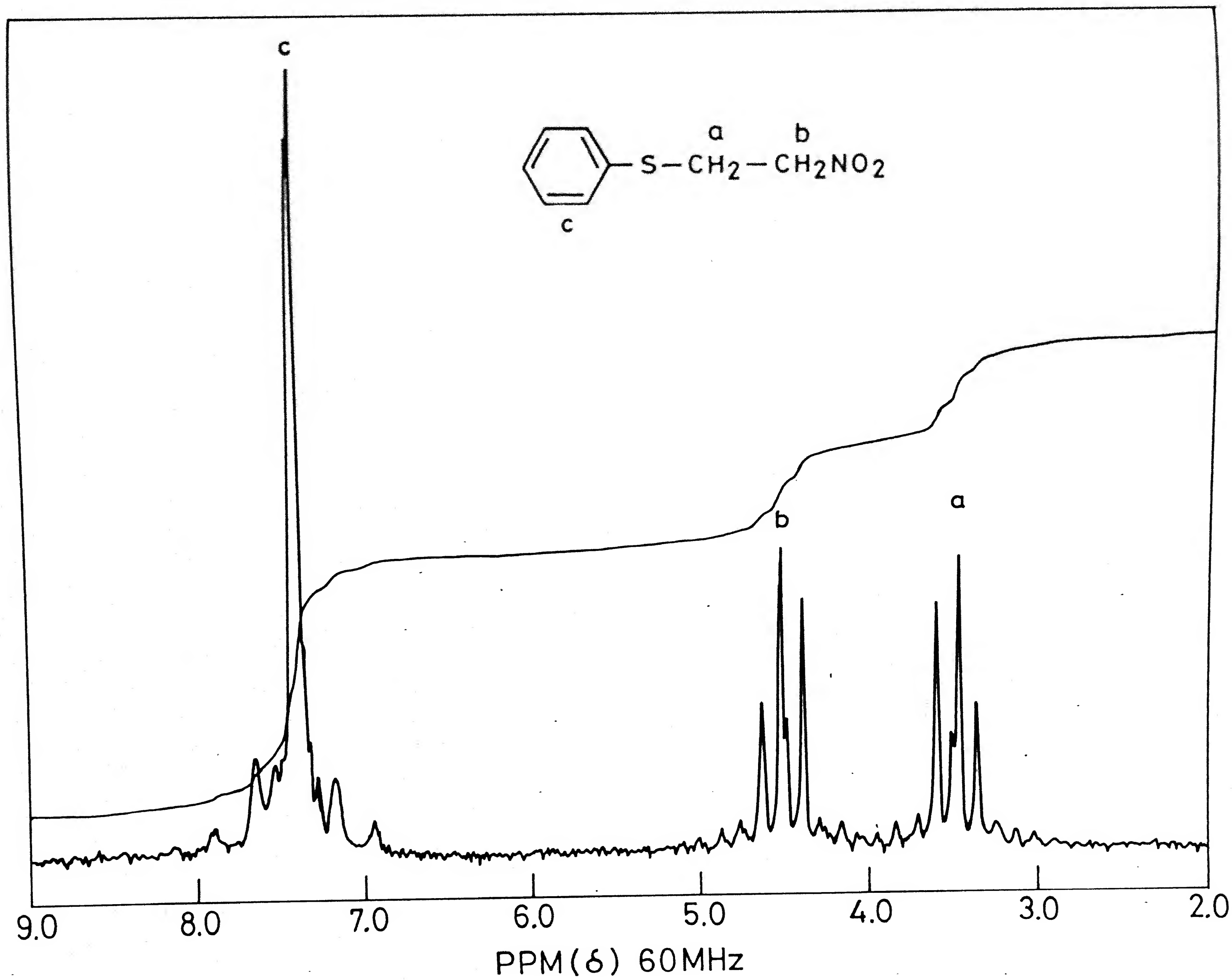


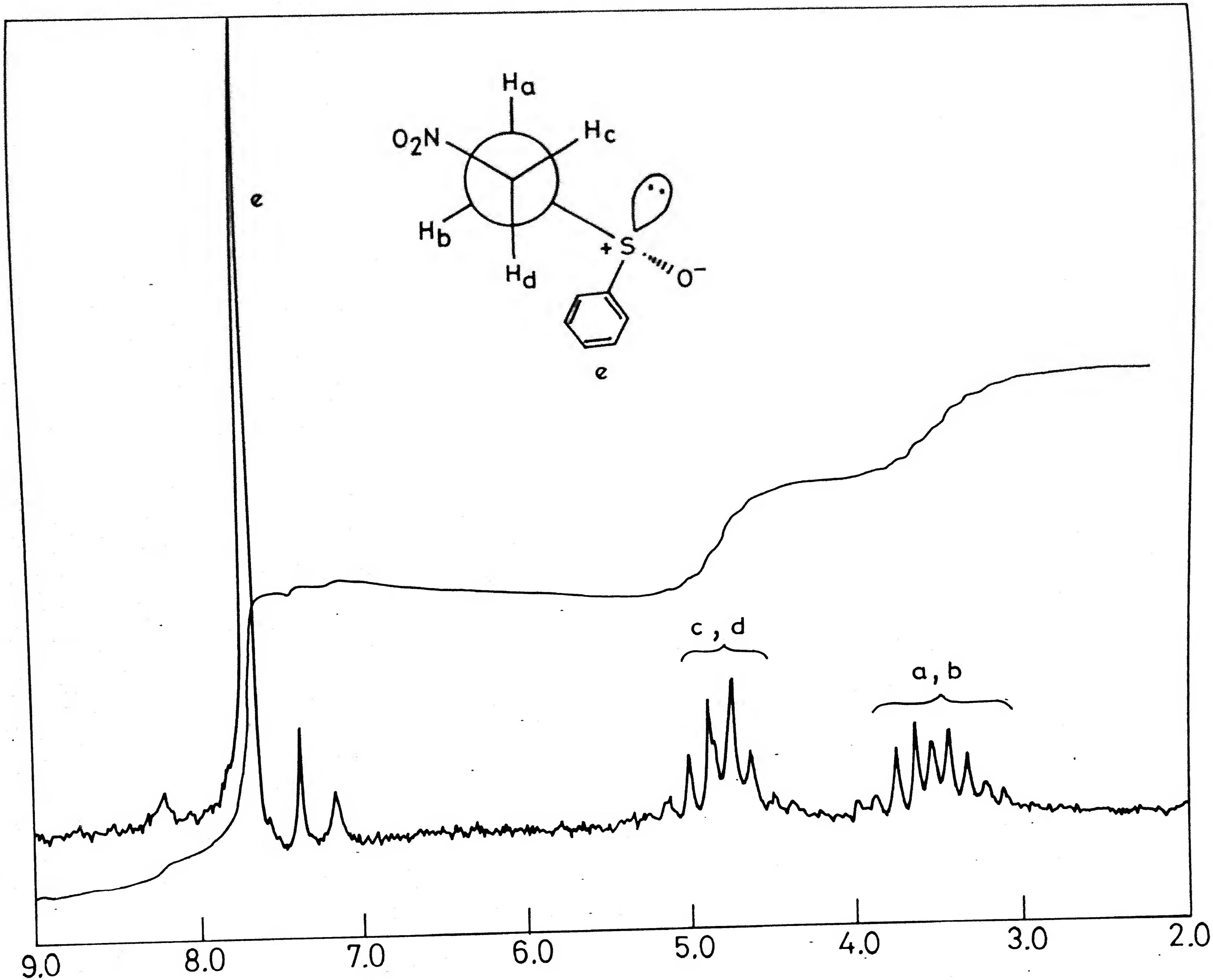
a
b
S—CH2—CH2Cl
c
c
a+b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz



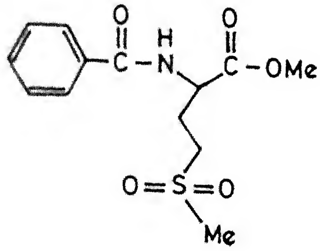
a + b
c
a
b
S–CH2–CH2Br
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
PPM (δ) 60MHz

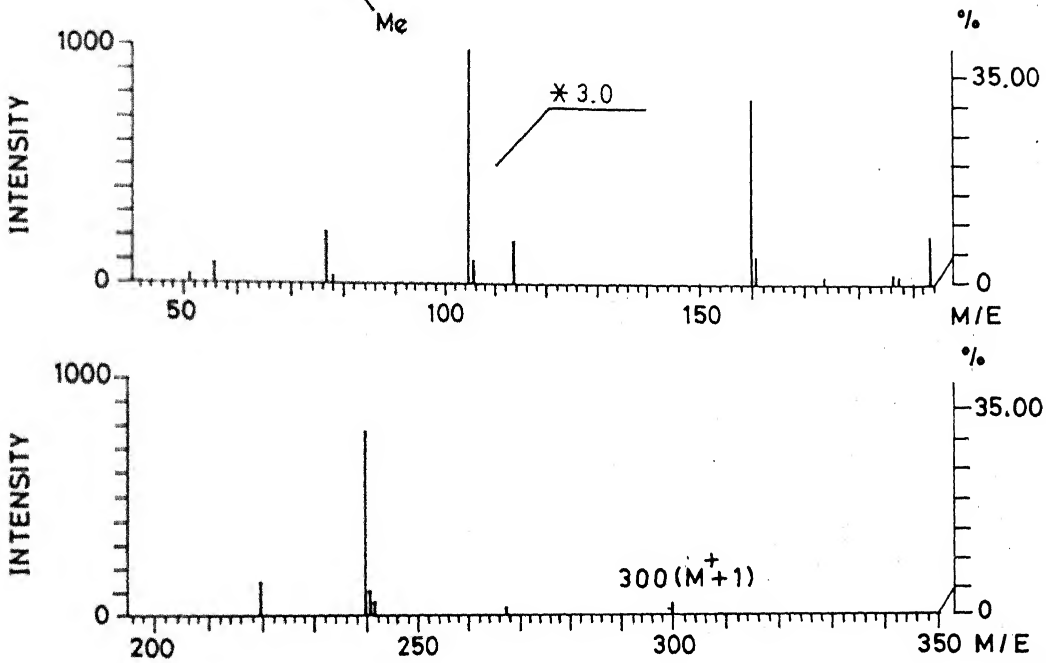

a
b
c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60MHz

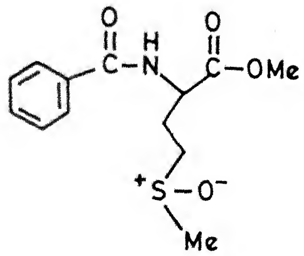

c
a
b
S—CH2—CH2NO2
c
b
a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM(δ) 60MHz

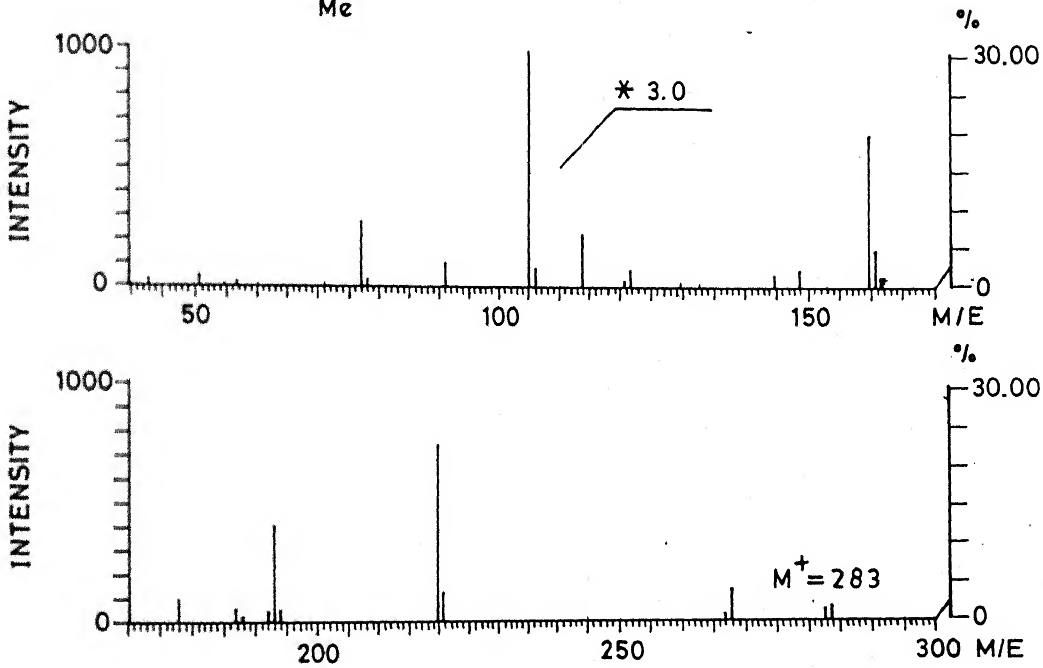


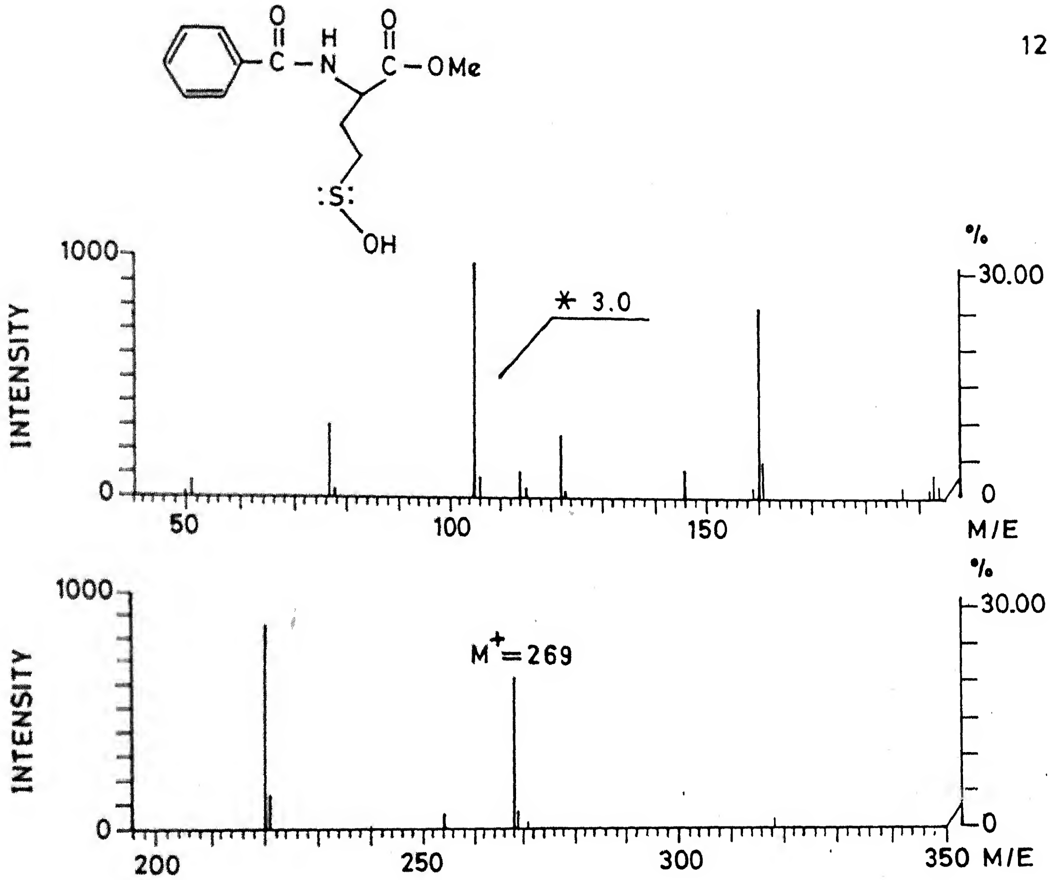
Ha
Hc
O2N
Hb
Hd
+S
O⁻
e
e
c , d
a , b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0



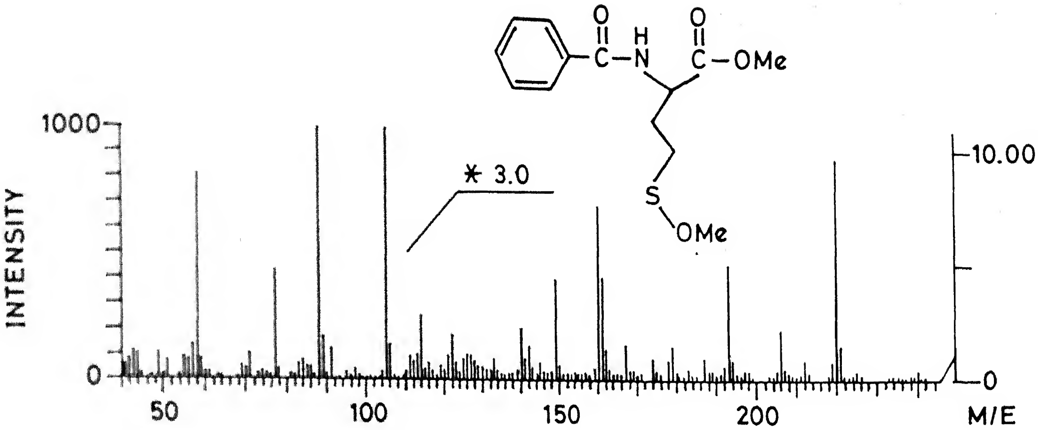

1000
INTENSITY
0
%
35.00
0
✻3.0
50
100
150
M/E
1000
INTENSITY
0
%
35.00
0
300(M$^+$+1)
200
250
300
350 M/E

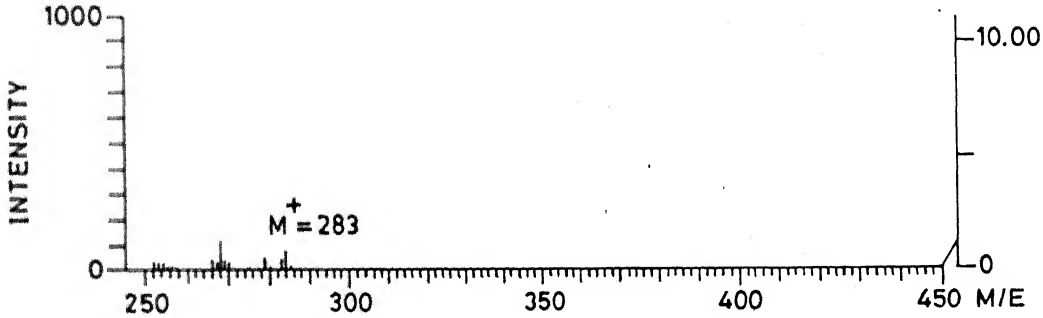


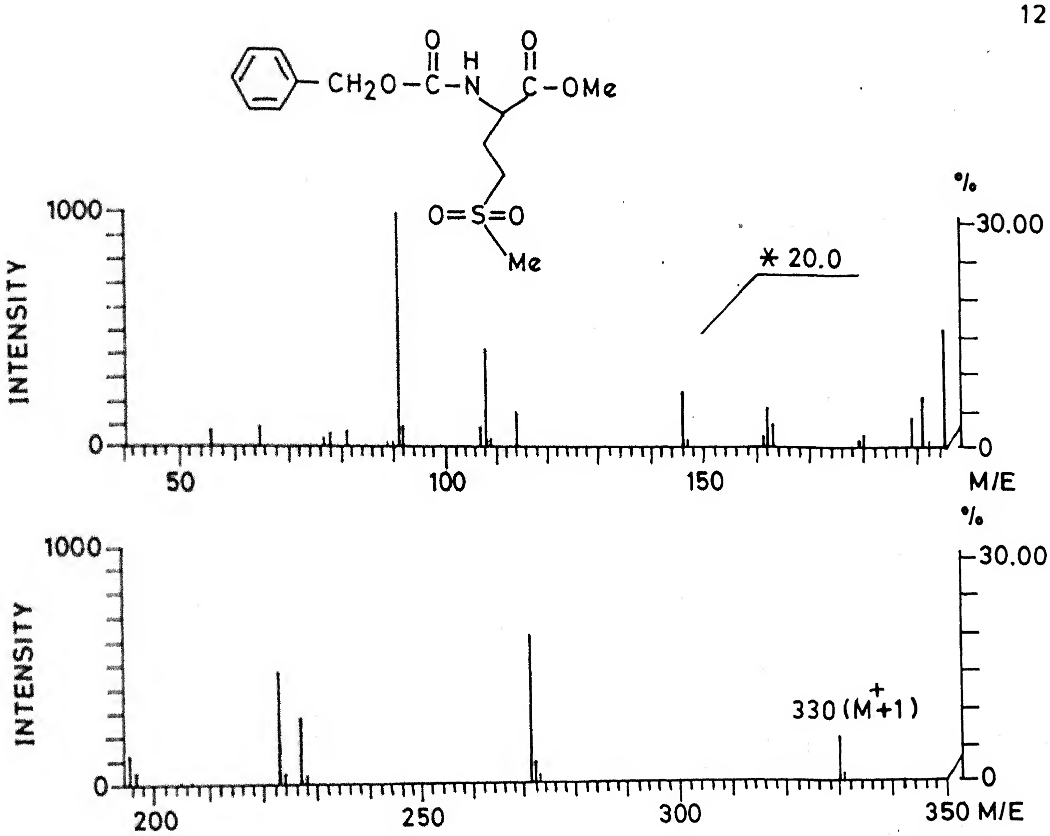

1000
0
INTENSITY
%
30.00
0
* 3.0
50
100
150
M/E
1000
0
INTENSITY
%
30.00
0
M+= 283
200
250
300 M/E



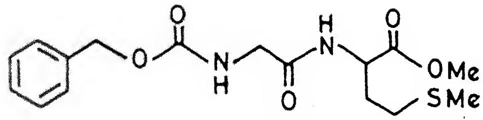
OMe
:S:
OH
1000
0
INTENSITY
%
30.00
0
* 3.0
50
100
150
M/E
M+=269
200
250
300
350

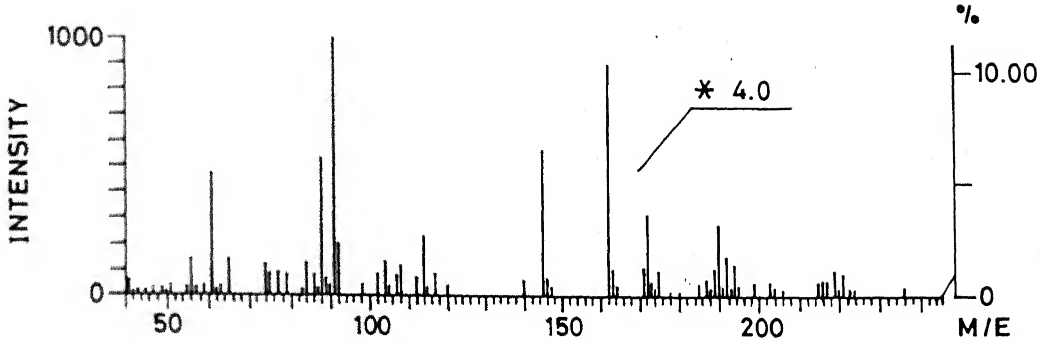

OMe
S
OMe
1000
INTENSITY
0
* 3.0
10.00
0
50
100
150
200
M/E

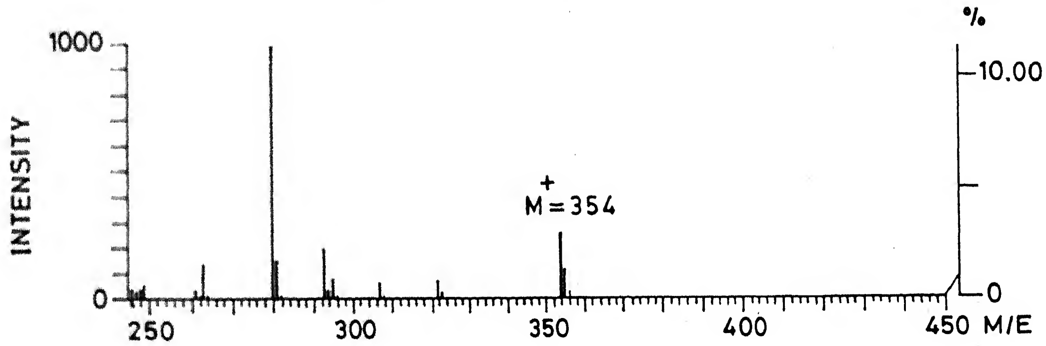

1000
INTENSITY
0
M+ = 283
10.00
0
250
300
350
400
450
M/E

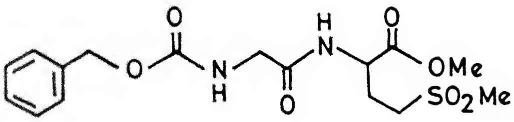


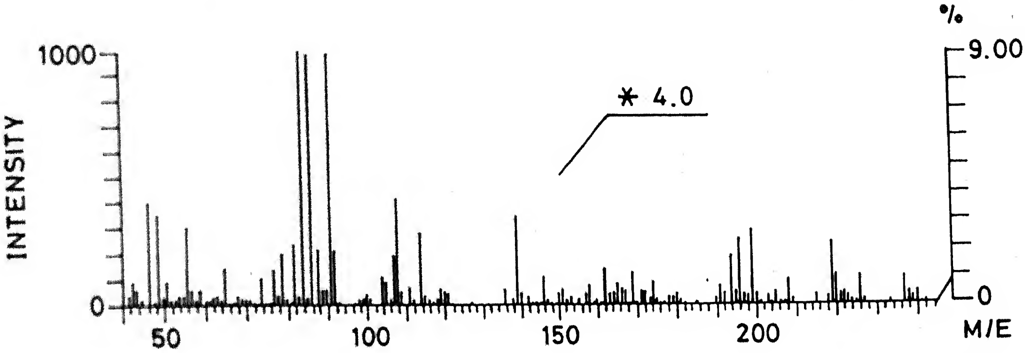
CH2O-C-N
C-OMe
O=S=O
Me
INTENSITY
1000
0
50
100
150
M/E
%
30.00
* 20.0
330 (M+1)
200
250
300
350 M/E

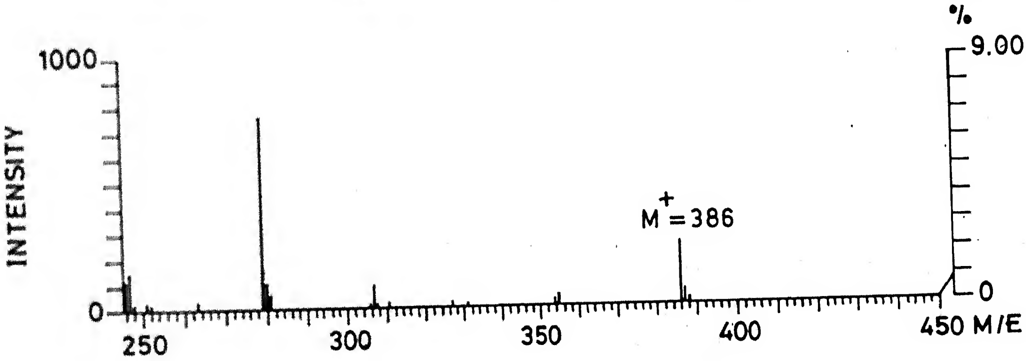

O
O
H
N
N
H
O
OMe
SMe

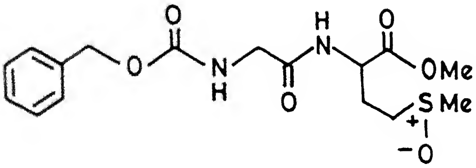

1000
0
INTENSITY
50
100
150
200
M/E
%
10.00
0
* 4.0

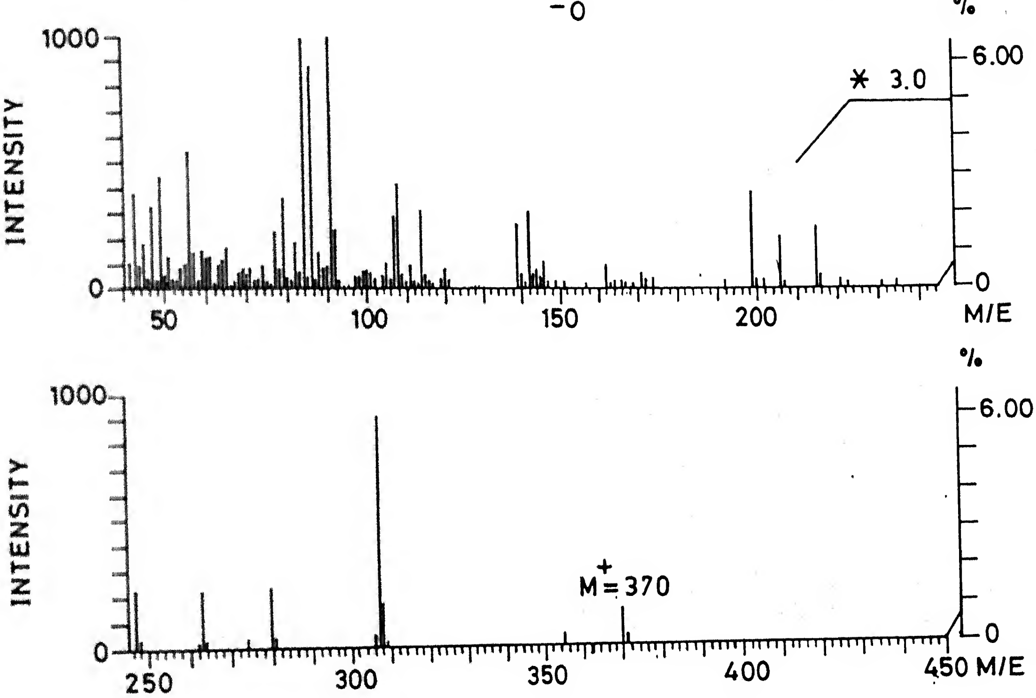

1000
0
INTENSITY
M = 354
250
300
350
400
450
M/E
%
10.00
0

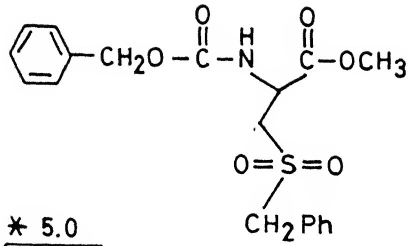

O
H
N
O
N
H
O
OMe
SO_2Me

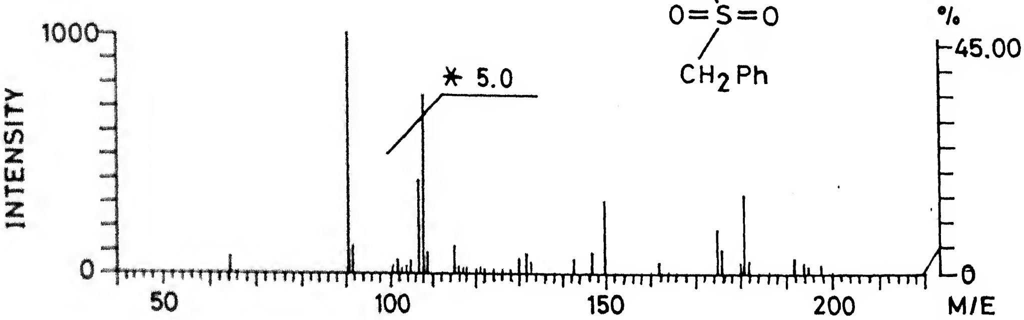

INTENSITY
1000
0
%
9.00
0
* 4.0
50
100
150
200
M/E


INTENSITY
1000
0
%
9.00
0
M+=386
250
300
350
400
450 M/E

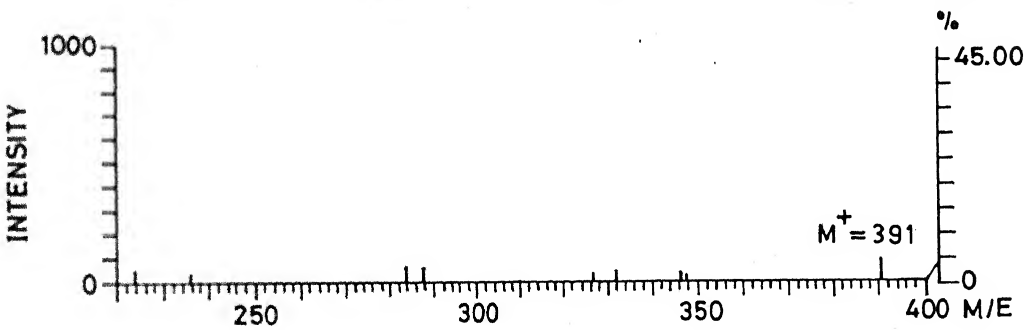

OMe
S Me
O


INTENSITY
1000
0
50
100
150
200
M/E
%
6.00
0
* 3.0
INTENSITY
1000
0
250
300
350
400
450 M/E
%
6.00
0
M+ = 370

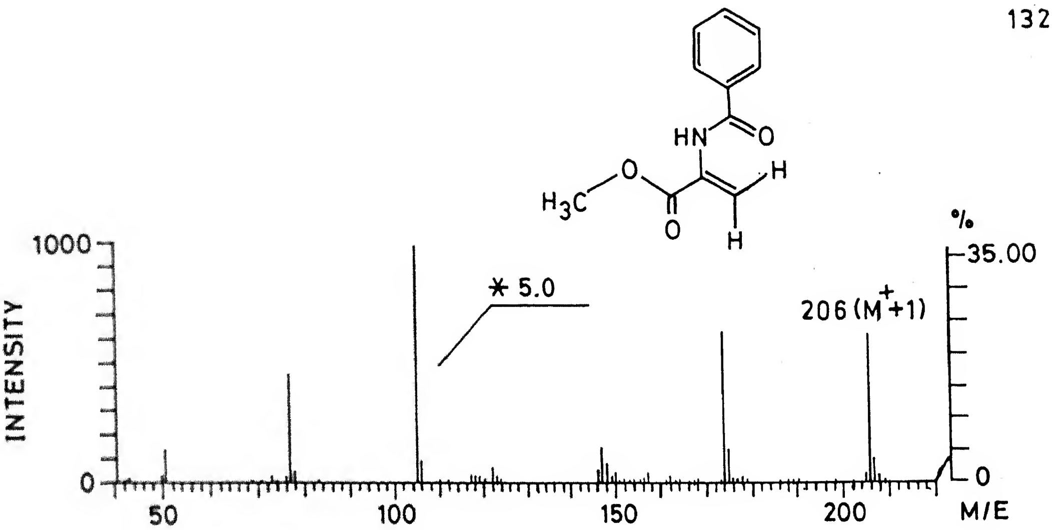


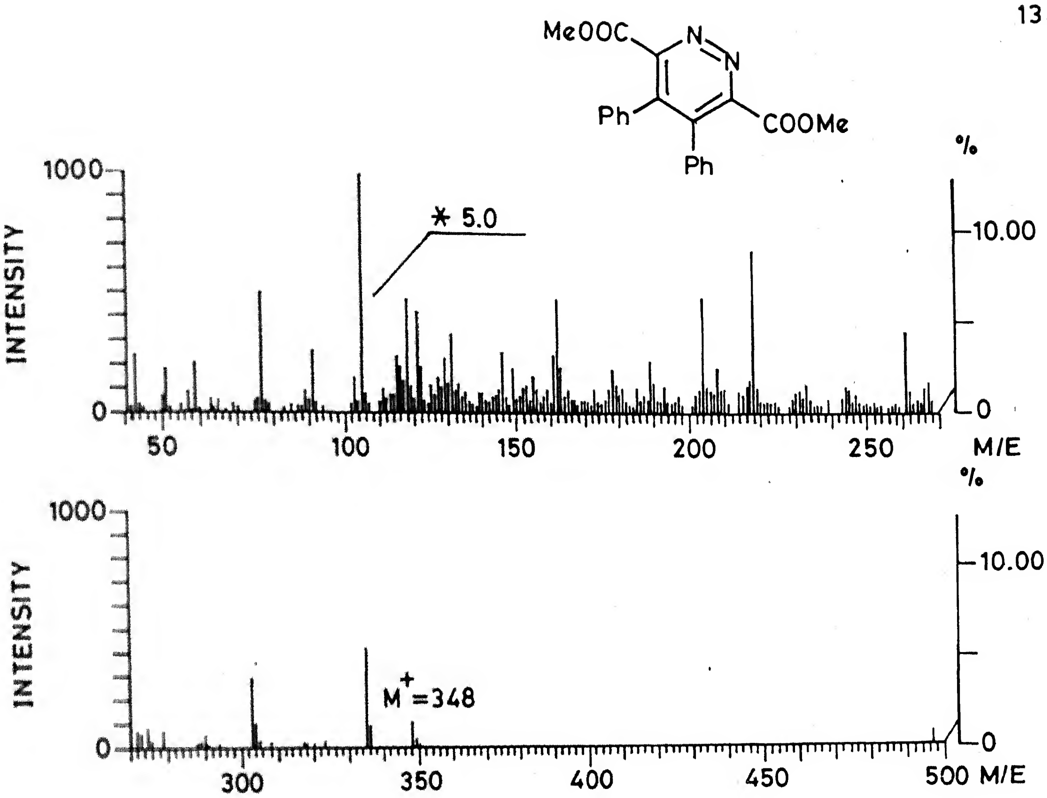


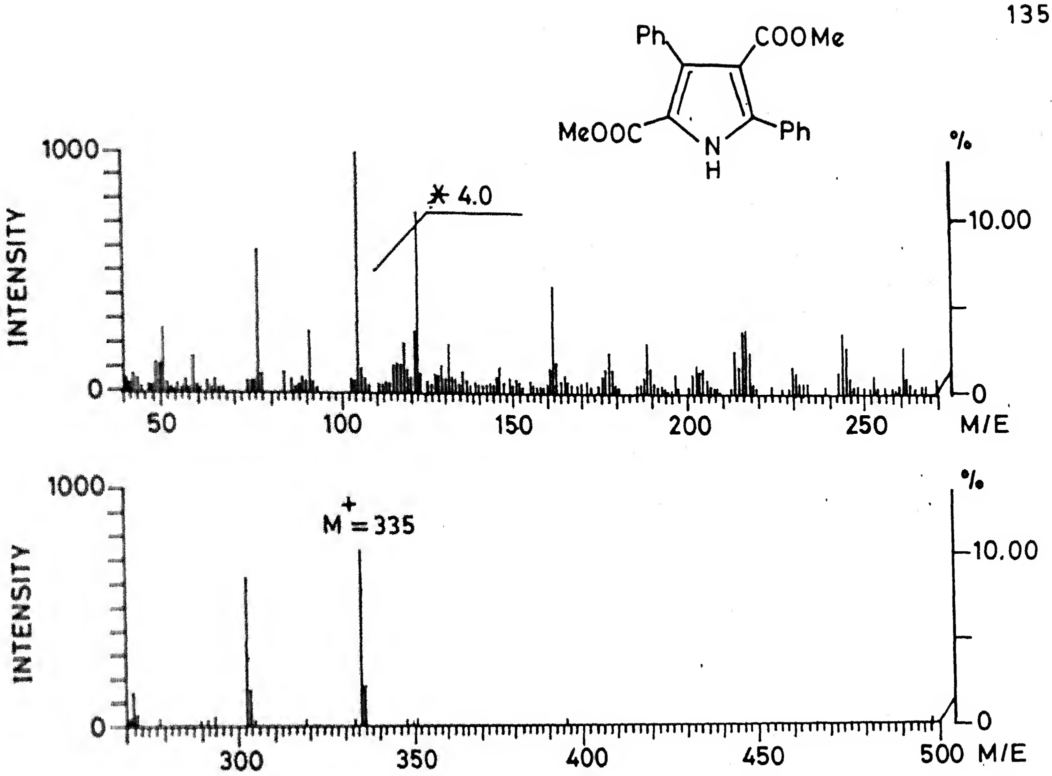
1000
0
INTENSITY
* 5.0
%
45.00
0
50
100
150
200
M/E



1000
0
INTENSITY
%
45.00
0
M+ = 391
250
300
350
400
M/E


HN
O
H
H3C
O
O
H
%
1000
0
INTENSITY
★ 5.0
206 (M+1)
35.00
0
50
100
150
200
M/E


MeOOC
N
N
Ph
COOMe
Ph
1000
INTENSITY
* 5.0
%
10.00
0
50
100
150
200
250
M/E
M+=348
300
350
400
450
500 M/E


Ph
COOMe
MeOOC
Ph
N
H
1000
INTENSITY
0
✱ 4.0
%
10.00
0
50
100
150
200
250
M/E
1000
INTENSITY
0
M⁺=335
%
10.00
0
300
350
400
450
500 M/E

E. EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 580 spectrophotometer either as neat liquids or as thin KBr discs. NMR spectra were obtained on 10-15% solutions in $CDCl_3$ or CCl_4 on a FT-R-600 instrument. The chemical shifts are recorded in ppm with TMS at 0.00 as internal standard. Mass spectra were obtained on a Jeol instrument. Elemental analyses were carried out in automatic C, H, N analysers. Silica gel G(ACME) was used for tlc and also for column chromatography (100-200 mesh). Reactions were monitored wherever possible by TLC. The organic extracts were invariably dried over anhydrous $MgSO_4$ and solvents evaporated *in vacuo*.

I. Preparation of 4-^{t}Butyl Iodoxybenzene (1)

a. 4-^{t}Butyl Iodobenzene (2):

A mixture of t-butyl benzene[45] (8 g, 59 mmol), iodine (6.35 g, 25 mmol), iodic acid (1.95 g, 111 mmol), glacial acetic acid (18 ml) and water (3 ml) was refluxed for 8 h, cooled to rt, decanted, the decanted portion admixed with water (30 ml) + methanolic potassium hydroxide (20%, 30 ml), refluxed for 0.5 h, cooled, the separated lower layer of 4-^{t}butyl iodobenzene washed with water (x 3), dried ($MgSO_4$) and fractionated to give 11 g (71%) of 4-^{t}butyl iodobenzene (2), bp 114°C/0.05 torr.

ir : ν_{max} (neat) cm^{-1}: 1500, 1400, 1370, 1270, 820, 720.

nmr : δ (CCl_4), 60 MHz: 1.3 (s, 9 H, tert-butyl), 7.03 (d, J = 8 Hz, 2 H, aromatic), 7.52 (d, J = 8 Hz, 2 H, aromatic).

b. 4-^{t}Butyl Iodobenzene Dichloride (3):

Dry chlorine was passed through an ice-salt cooled and vigorously stirred solution of 4-^{t}butyl iodobenzene (2.6 g, 1 mmol) in dry hexane (15 ml) till an excess was present (~3 h). The yellow crystalline 4-^{t}butyl iodobenzene dichloride (3) was filtered, washed sparingly with chilled hexane and dried. Yield 3.2 g (97%), mp 84°C, stable, soluble in chloroform and benzene.

ir : ν_{max} (KBr) cm^{-1}: 1510, 1410, 1280, 830, 560.

nmr : $\delta(CDCl_3)$, 60 MHz: 1.36 (s, 9 H, tert-butyl), 7.46 (d, J = 8 Hz, 2 H, aromatic), 8.06 (d, J = 8 Hz, 2 H, aromatic).

c. 4-^{t}Butyl Iodoxybenzene (1)

A floating yellow suspension of 4-^{t}butyl iodobenzene dichloride (3) (10 g, 30 mmol) on freshly prepared aqueous NaOCl (75 ml, prepared from 75 ml, 5 N NaOH and 12 g Cl_2) and glacial acetic acid (0.2 ml) was maintained at rt for 1.5 h, with intermittant shaking when a heavy yellow precipitate was formed. The mixture was kept at 60-70^{o}C, with intermittant shaking, for additional 0.5 h, during which froathing takes place and the heavy yellow precipitate transformed to light, white, 4-^{t}butyl iodoxybenzene (1). The reaction mixture was cooled in an ice bath, filtered, washed thoroughly with water, chloroform (50 ml), air dried and finally dried in a vacuum desiccator to give 7.5 g (86%) of 4-^{t}butyl iodoxybenzene (1), mp 217-221^{o}C (explodes!).

ir : ν_{max} (KBr) cm^{-1}: 1620, 1490, 1470, 825, 550.

Anal. Calcd. for $C_{10}H_{13}IO_2$ (Mol. wt. 292):

C, 41.09; H, 4.45%.

Found: C, 40.80; H, 4.31%.

II. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with Bis-Cyclohexylidene: Isolation of Cyclohexanone:

Bis-Cyclohexylidene

a. Cyclohexanone Azine:

To a stirred solution of cyclohexanone (25 g, 255 mmol) in ethanol (60 ml) was added, during 20 min, a solution of hydrazine hydrate (98%, 6.2 g) in ethanol (15 ml). The mixture was gently refluxed for 3 h, cooled, stored at 17°C for 16 h, solvents evaporated, poured on to water (150 ml), extracted with ether, dried ($MgSO_4$), solvents evaporated and the residue on crystallisation from hexane gave 32 g (66%) of cyclohexanone azine, mp 29-31°C (lit.[46] mp 32-32.5°C).

b. Cyclohexanespiro-2'-1',3',4'-thiadiazolidine-5'-spiro-cyclohexane

Gaseous hydrogen sulfide was passed through an ice cooled and stirred solution of cyclohexanone azine (2.51 g, 13 mmol) in acetone:benzene (1:1, 10 ml) till an excess was present (~3 h). Solvents were evaporated to yield 2.5 g (84%) of thia-diazolidine, mp 91°C (lit.[46] mp 91-93°C).

c. 2',5'-Dihydrocyclohexane Spiro-2'-1',3',4'-thiadiazine-5'-spirocyclohexane:

Powdered calcium carbonate (6 g) was suspended in hexane (bp 60-80°C, 100 ml), admixed with freshly prepared lead

tetraacetate[47] (6 g) and left stirred at 0° for 0.25 h. To this ice-cooled and stirred suspension was added, in drops, a solution of the above thiadiazolidine (2 g, 9 mmol) in hexane (100 ml). The mixture was allowed to warm to 18°, left stirred for a further 1.5 h, decomposed with saturated $NaHCO_3$ (100 ml), filtered; the organic layer, dried ($MgSO_4$), solvents evaporated and the residue on crystallization from hexane gave 1.6 g (80%) of azo-sulfide product, mp 78-79°C (lit.[46] mp 80-81°C).

ir : ν_{max} (KBr) cm^{-1}: 1575.

d. Bis-cyclohexylidene:

An intimate mixture of the above azo-sulfide (1.22 g, 5 mmol) and triphenylphosphine (1.58 g, 6 mmol) was held at 100°C for 2 h, cooled and chromatographed on silica gel. Elution with hexane gave 0.65 g (73%) of bis-cyclohexylidene, mp 51-53°C (lit.[48] mp 54-55°C).

e. Reaction of bis-cyclohexylidene with (1): Isolation of cyclohexanone:

A stirred mixture of 4-^{t}butyl iodoxybenzene (0.730 g, 2.5 mmol) and bis-cyclohexylidene (0.328 g, 2 mmol) and chlorobenzene (10 ml) was held at 130°C for 2 h, cooled and chromatographed on silica gel. Elution with hexane gave 0.6 g (91%) of 2 and with hexane:benzene (1:1) 0.231 g (59%) of cyclohexanone characterised as its 2:4-DNP derivative mp 158-159°C, whose

ir was identical to that of an authentic sample (lit.[49] mp 162°C).

III. Reaction of 4-^{t}Butyl Iodoxybenzene with E-Stilbene: Isolation of Benzaldehyde and Benzil:

A stirred mixture of 4-^{t}butyl iodoxybenzene (1) (0.584 g, 2 mmol) and E-stilbene (0.180 g, 1 mmol) in chlorobenzene (8 ml) was held at 140°C for 6 h, cooled and chromatographed on silica gel. Elution with hexane gave 0.5 g (94%) of 2 and with hexane:benzene (1:1) 0.142 g (67%) of benzaldehyde-characterised as its 2:4 DNP derivative mp 240°C whose ir was identical to that of an authentic sample and with benzene:ethylacetate (9:1) 0.041 g (20%) of benzil, mp 93°C (lit.[50] 94-95°C).

IV. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with 9-Benzylidene Fluorene: Isolation of Fluorenone and Benzaldehyde:

A stirred mixture of 4-^{t}butyl iodoxybenzene (1) (0.146 g, 0.5 mmol), 9-benzylidene fluorene (0.127 g, 0.5 mmol) and chlorobenzene (8 ml) was held at 170-180°C for 7 h. Chromatography on silica gel and elution with hexane gave 2 (92%), with hexane:benzene (19:1), 0.045 g (50%) of fluorenone, mp 83°C (lit.[51] mp 82-85°C) followed by 0.024 g (45%) of benzaldehyde characterised as its 2:4-DNP derivative, mp 239-240°C. The ir was identical to that of an authentic sample.

ir : ν_{max} (KBr) cm^{-1}: 1710 (C=O), fluorenone.

ir : ν_{max} (KBr) cm^{-1}: 1630, 1595, 1425, 2:4 DNP derivative.

V. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with Diphenyl Acetylene in Nitrobenzene: Isolation of Benzil:

A stirred mixture of 4-^{t}butyl iodoxybenzene (1) (0.438 g, 1.5 mmol), diphenyl acetylene (0.178 g, 1 mmol) and nitrobenzene (2 ml) was held at 140-170°C for 10 h, cooled and chromatographed on silica gel. Elution with hexane:benzene (1:9) gave 0.119 g (57%) of benzil, mp 92-94°C (lit.[50] mp 94-95°C). The ir was identical to that of an authentic sample.

ir : ν_{max} (KBr) cm^{-1}: 1660 (C=O), 1590, 1580, 1445, 1210, 1170.

VI. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with Diphenyl Acetylene in Chlorobenzene: Isolation of Benzil:

A stirred mixture of 4-^{t}butyl iodoxybenzene (1.168 g, 4 mmol), diphenyl acetylene (0.356 g, 2 mmol) and chlorobenzene (8 ml) was held at 140-170°C for 18 h, cooled, chlorobenzene evaporated *in vacuo* and the residue chromatographed on silica gel. Elution with hexane gave 2 (91%) and with hexane:benzene (1:9) 0.275 g (66%) of benzil, mp 94°C (lit.[50] mp 94-95°C). The ir was identical to that of an authentic sample.

ir : ν_{max} (KBr) cm^{-1}: 1660 (C=O), 1590, 1580, 1445, 1210, 1170.

VII. Reaction of 4-^{t}Butyl Iodoxybenzene with Phenanthrene: Isolation of 9,10-Phenanthrenequinone:

A stirred mixture of 4-^{t}butyl iodoxybenzene (0.584 g, 2 mmol), phenanthrene (0.178 g, 1 mmol) and chlorobenzene (5 ml) was held at 130-140°C for 10 h, cooled, chlorobenzene evaporated and the residue chromatographed over silica gel. Elution with hexane gave 4-^{t}butyl iodobenzene (2) 0.531 g (97%) and with benzene:ethyl acetate(9:1) 0.156 g (75%) of 9,10-phenanthrenequinone which was crystallised from ethanol, mp 208°C (lit.[52] mp 209-211°C). The ir spectrum was identical to that of an authentic sample.

ir : ν_{max} (KBr) cm^{-1}: 1670 (C=O), 1590, 1450, 1280.

VIII. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with Anthracene: Isolation of 9,10-Anthraquinone:

A stirred mixture of 4-^{t}butyl iodoxybenzene (0.292 g, 1 mmol) anthracene (0.089g, 0.5 mmol) and nitrobenzene (4 ml) was held at 130°C for 7 h, cooled and chromatographed on silica gel. Elution with hexane:benzene (1:4) gave 0.061 g (59%) of anthraquinone which on crystallisation from benzene gave pale yellow needles, mp 282°C (lit.[53] mp 284-285°C), the ir of which was identical to that of authentic sample.

ir : ν_{max} (KBr) cm^{-1}: 1662 (C=O), 1275, 930, 805, 685.

IX. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with Tetralin: Isolation of α-Tetralone:

A stirred mixture of 4-^{t}Butyl iodoxybenzene (0.438 g, 1.5 mmol), tetralin (1.32 g, 10 mmol) and chlorobenzene (10 ml) was held at 140^{o}C for 6 h, cooled, chlorobenzene evaporated *in vacuo* and the residue chromatographed on silica gel. Elution with hexane gave 2 (97%) and with benzene:hexane (1:1) 0.130 g (60%) of α-tetralone whose ir and nmr were identical to that of an authentic sample. In this experiment 0.5 g of unchanged tetralin was isolated.

ir : ν_{max} (neat) cm^{-1}: 1675 (C=O).

nmr : δ (CCl_4), 60 MHz: 2.45 (m, 6 H, methylene protons), 7.45 (m, 4 H, aromatic).

X. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with Camphene in nitrobenzene: Isolation of camphenilone

A stirred mixture of 4-^{t}butyl iodoxybenzene (0.292 g, 1 mmol), camphene (0.068 g, 0.5 mmol) and nitrobenzene (5 ml) was held at 145^{o}C for 8 h, cooled and chromatographed on silica gel. Elution with hexane:benzene (1:1) gave 0.043 g (63%) of camphenilone whose ir was identical to that of an authentic sample.[54]

ir : ν_{max} (neat) cm^{-1}: 1740 (C=O), 1660, 1470.

XI. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with Camphene in Chlorobenzene: Isolation of Camphenilone:

A stirred mixture of 4-^{t}Butyl iodoxybenzene (0.292 g, (1 mmol), camphene (0.136 g, 1 mmol) and chlorobenzene (5 ml) was held at 140-160^{o}C for 10 h, cooled, chlorobenzene evaporated and the residue chromatographed on silica gel. Elution with hexane gave unchanged camphene (0.036 g) and with benzene: hexane (1:1) 0.065 g (48%) of camphenilone whose ir was identical to that of an authentic sample.[54]

ir : ν_{max}(neat) cm^{-1}: 1740 (C=O).

XII. Reaction of 4-^{t}Butyl Iodoxybenzene (1) Supported on Silica gel with Aniline: Isolation of Azobenzene:

A slurry of 4-^{t}butyl iodoxybenzene (0.438 g, 1.5 mmol), aniline (0.093 g, 1 mmol), activated silica gel (20 g, 100-200 mesh) and methylene dichloride (25 ml) was maintained at 0^{o}C, with intermittant shaking for 10-20 min. The reaction mixture was allowed to warm to rt and put on the column. Elution with benzene:ethyl acetate (1:1) gave 0.082 g (67%) of azobenzene which was crystallised from aqueous ethanol, mp 60^{o}C. The ir spectrum was identical to that of an authentic sample.

ir : ν_{max} (KBr) cm^{-1}: 1590 (-N=N-), 1550, 1490, 1460, 940, 790.

nmr : δ ($CDCl_3$), 60 MHz: 7.39 (m, 6 H, 3,5,3',5',4,4'-m,p-aromatic protons), 7.8 (m, 4 H, 2,6,2',6'-o-aromatic protons).

XIII. <u>Reaction of 4-^{t}Butyl Iodoxybenzene (1) with N-Benzoyl Methionine Methyl Ester (4): Isolation of Sulfone (5) Sulfoxide (6), Sulfenic Acid (7), N-Benzoyl Aspartic Acid Dimethyl Ester (8) and Sulfenic Ester (9):</u>

A stirred solution of 4 (0.801 g, 3 mmol) in chlorobenzene (20 ml) was admixed with 4-^{t}butyl iodoxybenzene (1.314 g, 4.5 mmol), refluxed for 3.5 h until clear solution was obtained, cooled, solvents evaporated *in vacuo*, the residue triturated with a saturated solution of sodium bicarbonate (20 ml) for 3 h, extracted with ethyl acetate (3 x 15 ml), the ethyl acetate extract combined, dried ($MgSO_4$), solvents evaporated and the residue (1.5 g) chromatographed over silica gel. Elution with hexane gave 0.680 g (59%) of 4-^{t}butyl iodobenzene and with benzene:ethylacetate (3:7), 0.255 g (29%) of (5) which on crystallisation from benzene:hexane gave white crystals, mp 106^{o}C.

ir : ν_{max} (KBr) cm^{-1}: 3300 (NH), 1730 (C=O), 1630, 1520, 1290, 1230, 1120 (SO_2).

nmr : δ ($CDCl_3$), 60 MHz: 2.9 (s, 3 H, $SO_2C\underline{H}_3$), 3.0-3.41 (m, 4 H, $-C\underline{H}_2C\underline{H}_2-$), 3.75 (s, 3 H, $COOC\underline{H}_3$), 4.9 (q, 1 H, tert-proton), 7.1-7.9 (m, 5 H, aromatic).

m/z : 299 (M^+), 240 (M^+ - COOMe), 220 (M^+ - SO_2Me), 161 [M^+ - (COOMe + SO_2Me)], 194 (M^+ - COPh).

Anal. Calcd. for $C_{13}H_{17}NO_5S$ (Mol. wt. 299):

C, 52.17; H, 5.68; N, 4.68%.

Found: C, 51.68; H, 5.39; N, 4.37%.

Further elution with benzene:ethyl acetate (3:7) gave 0.085 g (11%) of (7) which on crystallisation from benzene: hexane gave white needles, mp 132°C.

ir : ν_{max} (KBr) cm^{-1}: 3300 (NH), 1725 (C=O), 1525, 1320, 1240, 1030, 700.

nmr : δ ($CDCl_3$), 60 MHz: 2.8-3.25 (m, 4 H, $-C\underline{H}_2C\underline{H}_2-$). 3.8 (s, 3 H, $-COOC\underline{H}_3$), 4.9 (q, 1 H, tert-proton), 7.20-8.12 (m, 5 H, aromatic).

m/z : 269 (M^+), 268 (M^+ - 1), 220 (M^+ - SOH).

Anal. Calcd. for $C_{12}H_{15}NO_4S$ (Mol. wt. 269):

C, 53.53; H, 5.57; N, 5.20%.

Found: C, 53.42; H, 5.36; N, 5.08%.

Finally, elution with benzene:ethyl acetate (1:4) gave 0.304 (36%) of (6) as a colorless thick liquid.

ir : ν_{max} (neat) cm^{-1}: 3300 (NH), 1730 (C=O), 1635, 1525, 1220, 1030 (SO).

nmr : δ ($CDCl_3$), 60 MHz: 2.56 (s, 3 H, $SOC\underline{H}_3$), 2.63-3.10 (m, 4 H, $-C\underline{H}_2C\underline{H}_2-$), 3.73 (s, 3 H, $COOC\underline{H}_3$), 4.85 (q, 1 H, tert-proton), 7.3-8.0 (m, 5 H, aromatic).

m/z : 283 (M^+), 284 (M^+ + 1).

Anal. Calcd. for $C_{13}H_{17}NO_4S$ (Mol. wt. 283):

C, 55.12; H, 6.00; N, 4.94%.

Found: C, 55.25; H, 6.13; N, 4.56%.

The bicarbonate extract (vide supra) was cooled, filtered, acidified with 2 N H_2SO_4, saturated with solid sodium chloride and extracted with ethyl acetate (3 x 15 ml). The ethyl acetate extracts were combined, dried ($MgSO_4$), solvents evaporated *in vacuo*, the residue (0.201 g), esterified with diazomethane and chromatographed over silica gel, elution with benzene:ethyl acetate (3:2) gave 0.050 g (7%) of (8) whose ir and nmr was identical to that of an authentic sample.[55]

ir : ν_{max} (neat) cm^{-1}: 3320 (NH), 1725 (ester), 1670, 1470.

nmr : δ ($CDCl_3$), 60 MHz: 2.85-3.1 (m, 2 H, $-CH_2$), 3.6 (s, 3 H, β-$COOCH_3$), 3.7 (s, 3 H, α-$COOCH_3$), 4.82 (q, 1 H, tert-proton), 7.2-8.0 (m, 5 H, aromatic).

Further elution with benzene:ethyl acetate (1:1) gave 0.105 g (12%) of (9) as a thick yellow liquid.

ir : ν_{max} (neat) cm^{-1}: 3400 (NH), 1730 (ester), 1667, 1535, 1235, 1010, 725.

nmr : δ ($CDCl_3$), 60 MHz: 2.53 (s, 3 H, $SOCH_3$), 2.62-3.17 (m, 4 H, $-CH_2CH_2-$), 3.73 (s, 3 H, $COOCH_3$), 4.8 (q, 1 H, tert-proton), 7.3-8.07 (m, 5 H, aromatic).

m/z : 283 (M^+), 284 ($M^+ + 1$).

Anal. Calcd. for $C_{13}H_{17}NO_4S$ (Mol. wt. 283):

C, 55.12; H, 6.00; N, 4.94%.

Found: C, 55.07; H, 5.82; N, 4.61%.

XIV. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with N-Benzyloxycarbonyl Methionine Methyl Ester (13): Isolation of Sulfone (14) and Benzyl Carbamate (15):

To a stirred solution of (13) (0.240 g, 0.808 mmol) in chlorobenzene (15 ml) was added (1) (0.284 g, 0.972 mmol). The mixture was held at 140°C until the thick slurry completely dissolved (2.5 h). The mixture was cooled, solvents evaporated *in vacuo*, the residue triturated for 3 h with a saturated solution of sodium bicarbonate (20 ml), extracted with ethyl acetate (2 x 20 ml), the ethyl acetate extracts combined, dried ($MgSO_4$), solvents evaporated and the residue chromatographed over silica gel. Elution with hexane gave 0.180 g (72%) of 4-^{t}butyl iodobenzene (2) and with benzene:ethyl acetate (1:4), 0.044 g (36%) of benzyl carbamate (15) which on crystallisation from benzene gave white needles, mp 84°C.

ir : ν_{max} (KBr) cm^{-1}: 3410, 3200, 1685.

nmr : δ ($CDCl_3$), 60 MHz: 5.13 (s, 2 H, -OC$\underline{H}_2$Ph), 7.32 (s, 5 H, aromatic).

m/z : 151 (M^+), 107 ($M^+ - CONH_2$).

Further elution with benzene:ethyl acetate (1:1) gave 0.150 g (57%) of (<u>14</u>) which on crystallisation from hot benzene gave colorless prisms, mp 89^{o}C.

ir : ν_{max} (KBr) cm^{-1}: 3310 (NH), 1725, 1680 (C=O), 1520, 1310, 1240, 1120 (SO_2).

nmr : δ($CDCl_3$), 60 MHz: 2.38 (m, 2 H, $-CH_2\underline{CH_2}CH-$), 2.88 (s, 3 H, $SO_2\underline{CH_3}$), 2.93-3.38 (m, 2 H, $-CH_2\underline{CH_2}SO_2Me$), 3.76 (s, 3 H, $-COO\underline{CH_3}$), 4.53 (m, 1 H, tert-proton), 5.09 (s, 2 H, $-O\underline{CH_2}Ph$), 5.78 (d, 1 H, N<u>H</u>-CH-), 7.31 (s, 5 H, aromatic).

m/z : 329 (M^+), 330 (M^+ + 1), 191 (M^+ - COOMe - SO_2Me).

Anal. Calcd. for $C_{14}H_{19}NO_6S$ (Mol. wt. 329):

C, 51.06; H, 5.77; N, 4.25%.

Found: C, 50.84; H, 5.86; N, 4.01%.

XV. <u>Reaction of Z-Gly-Met-OMe (17) with 4-^{t}Butyl Iodoxybenzene (1): Isolation of Sulfone (18) and Sulfoxide (19):</u>

a. Met-OMe.HCl:

Thionyl chloride (7 ml, 95 mmol), in drops, followed by L-methionine (10.4 g, 70 mmol) was added to stirred and ice-cooled anhydrous methanol (70 ml). The reaction mixture was slowly allowed to attain rt, left stirred overnight, the clear solution evaporated and the residue on crystallisation from absolute methanol-dry ether gave 11.2 g (80%) of Met-OMe.HCl

as white needles, mp 149-150°C (lit.[56] mp 151°C).

b. Met-OMe:

Triethylamine (3.6 ml, 26 mmol) was added, in drops, to a stirred and ice-cooled solution of Met-OMe.HCl (5 g, 25 mmol) in dry CH_2Cl_2 (60 ml). The mixture was left aside for 0.5 h washed with cold water (2 x 30 ml), dried ($MgSO_4$), evaporated and the thick yellow residue of Met-OMe (3.3 g, 83%) was used as such in the following experiment.

c. Z-Gly-Met-OMe:

1-Hydroxybenzotriazole (HOBt) (1.35 g, 10 mmol) followed by DCC (2.1 g, 10 mmol) was added to a stirred solution of Z-Gly[67] (2.09 g, 10 mmol) in dry CH_2Cl_2 (20 ml). A solution of Met-OMe (1.63 g, 10 mmol) in dry CH_2Cl_2 (10 ml) was then added, the mixture left stirred overnight at rt, filtered, washed with CH_2Cl_2 (2 x 15 ml), the filtrate and washings evaporated, the residue dissolved in CH_2Cl_2, washed with 2 N HCl (2 x 15 ml), saturated $NaHCO_3$ (20 ml), saturated NaCl (2 x 30 ml), dried ($MgSO_4$), solvents evaporated <u>in vacuo</u> and the resulting thick yellow residue (3.2 g) chromatographed on silica gel.

Elution with ethyl acetate:benzene (1:1) gave 2.6 g (74%) of Z-Gly-Met-OMe (17) as a viscous liquid.

ir : ν_{max} (neat) cm^{-1}: 3350 (NH), 1740 (ester), 1680 (amide).

nmr : δ ($CDCl_3$), 60 MHz: 2.06 (s, 3 H, $SC\underline{H}_3$), 2.46 (m, 4 H, $-C\underline{H}_2C\underline{H}_2SCH_3$), 3.7 (s, 3 H, $-COOC\underline{H}_3$), 3.8-4.2 (m, 2 H, $-NHC\underline{H}_2CO-$), 4.7 (d, 1 H, tert-proton), 5.1 (s, 2 H, $-OC\underline{H}_2Ph$), 5.67 (br, 2 H, $-N\underline{H}-$), 7.3 (s, 5 H, aromatic).

m/z : 354 (M^+), 355 ($M^+ + 1$).

Anal. Calcd. for $C_{16}H_{22}N_2O_5S$ (Mol. wt. 354):

C, 54.23; H, 6.21; N, 7.90%.

Found: C, 54.01; H, 6.70; N, 7.76%.

d. Reaction of Z-Gly-Met-OMe (<u>17</u>) with (<u>1</u>):

To a stirred solution of (<u>17</u>) (1.416 g, 4 mmol) in chlorobenzene (30 ml) was added (<u>1</u>) (1.460 g, 5 mmol) at rt. The mixture was held at 80-90°C for 1.5 h, cooled, solvents evaporated <u>in vacuo</u> and the residue chromatographed over silica gel. Elution with ethyl acetate:methanol (98:2) gave 0.400 g (26%) of sulfone (<u>18</u>) as a thick syrupy liquid.

ir : ν_{max} (neat) cm^{-1}: 3340 (br, NH), 1735 (ester), 1680 (amide), 1300, 1140 (SO_2).

nmr : δ ($CDCl_3$), 60 MHz: 2.83 (s, 3 H, $-SO_2C\underline{H}_3$), 2.92-3.44 (m, 4 H, $-CHC\underline{H}_2C\underline{H}_2SO_2-$), 3.7 (s, 3 H, $COOC\underline{H}_3$), 3.77-4.72 (m, 3 H, $-C\underline{H}_2CONHC\underline{H}-$), 5.05 (s, 2 H, $-OC\underline{H}_2Ph$), 5.94 (br, 2 H, 2 x$N\underline{H}$), 7.26 (s, 5 H, aromatic).

m/z : 386 (M^+), 387 ($M^+ + 1$), 307 ($M^+ - SO_2CH_3$), 279 ($M^+ - OCH_2Ph$).

Anal. Calcd. for $C_{16}H_{22}N_2O_7S$ (Mol. wt. 386):

C, 49.74; H, 5.69; N, 7.25%.

Found: C, 49.69; H, 5.42; N, 7.24%.

Further elution with ethyl acetate:methanol (1:1) gave 0.0620 g (42%) of sulfoxide (19) as a thick syrupy liquid.

ir : ν_{max} (neat) cm^{-1}: 3320 (br, NH), 1740 (ester), 1670 (amide), 1045 (SO).

nmr : δ ($CDCl_3$), 60 MHz: 2.51 (s, 3 H, $SOC\underline{H}_3$), 2.58-3.28 (m, 4 H, $-CHC\underline{H}_2C\underline{H}_2SO-$), 3.7 (s, 3 H, $COOC\underline{H}_3$), 3.88 (m, 2 H, $-NHC\underline{H}_2CO-$), 4.78 (m, 1H, $-NHC\underline{H}CH_2-$), 5.08 (s, 2 H, $-OC\underline{H}_2Ph$), 5.98 (br, 2 H, 2 x$N\underline{H}$), 7.28 (s, 5 H, aromatic).

m/z : 370 (M^+), 307 (M^+ - $SOCH_3$), 263 (M^+ - OCH_2Ph).

Anal. Calcd. for $C_{16}H_{22}N_2O_6S$ (Mol. wt. 370):

C, 51.89; H, 5.94; N, 7.56%.

Found: C, 51.80; H, 5.62; N, 7.31%.

XVI. Reaction of 4-^{t}Butyl Iodoxybenzene (1) with N-Carbobenzoxy(S-benzyl)cysteine Methyl Ester (20): Isolation of Sulfone (21), Sulfoxide (22) and Azlactone (23):

A stirred solution of (20) (0.359 g, 1 mmol) in chlorobenzene (15 ml) was admixed with (1) (0.438 g, 1.5 mmol), refluxed for 1.5 h, cooled, solvents evaporated, the residue triturated with saturated aq. $NaHCO_3$ (30 ml) for 3.5 h,

extracted with ethyl acetate (3 x 20 ml), the ethyl acetate extracts combined, dried ($MgSO_4$), solvents evaporated and the residue chromatographed over silica gel. Elution with hexane gave 0.256 g (66%) of 2 and with benzene, 0.068 g (18%) of sulfone (21) which on crystallisation from benzene:hexane gave colourless crystals, mp 174°C.

ir : ν_{max} (KBr) cm^{-1}: 3315 (NH), 1730 (ester), 1685, 1300, 1250, 1130 (SO_2), 1050.

nmr : δ ($CDCl_3$), 60 MHz: 3.5 (d, 2 H, $SO_2C\underline{H}_2CH$-), 3.71 (s, 3 H, $COOC\underline{H}_3$), 4.2 (s, 2 H, $C\underline{H}_2Ph$), 4.72 (m, 1 H, tert-proton), 5.08 (s, 2 H, $OC\underline{H}_2Ph$), 5.9 (br, 1 H, N$\underline{H}$-), 7.3 (s, 10 H, aromatic).

m/z : 391 (M^+).

Anal. Calcd. for $C_{19}H_{21}NO_6S$ (Mol. wt. 391):

C, 58.31; H, 5.37; N, 3.58%.

Found: C, 58.22; H, 5.39; N, 3.22%.

Further elution with benzene:ethyl acetate (7:3) gave 0.111 g (30%) of sulfoxide (22) which was crystallised from hot benzene to give white needles, mp 119-121°C.

ir : ν_{max} (KBr) cm^{-1}: 3310 (NH), 1730 (ester), 1685, 1265, 1030 (SO).

nmr : δ ($CDCl_3$), 60 MHz: 3.06 (d, 2 H, -$SOC\underline{H}_2CH$-), 3.61 (s, 3 H, $COOC\underline{H}_3$), 3.91 (s, 2 H, $SOC\underline{H}_2Ph$), 4.57 (br,

1 H, CH-), 5.01 (s, 2 H, OCH_2Ph), 6.11 (br, 1 H, NH-), 7.2 (s, 10 H, aromatic).

m/z : 375 (M^+), 236 (M^+ - $SOCH_2Ph$).

Anal. Calcd. for $C_{19}H_{21}NO_5S$ (Mol. wt. 375).

C, 60.80; H, 5.60; N, 3.73%.

Found: C, 60.28; H, 5.77; N, 3.43%.

Finally elution with benzene:ethyl acetate (7:3) gave 0.025 g (8%) of azlactone (23) which on crystallisation from benzene gave colorless crystals, mp 112-114°C.

nmr : δ ($CDCl_3$), 60 MHz: 3.04 (m, 2 H, $SOCH_2$-C(=)(N)), 3.93 (s, 2 H, $SOCH_2Ph$), 4.97 (s, 2 H, OCH_2Ph), 7.2 (s, 10 H, aromatic).

The $NaHCO_3$ extract was cooled, filtered, acidified with 2 H_2SO_4, saturated with solid NaCl and extracted with ethyl acetate (3 x 20 ml). The ethyl acetate extracts were combined, dried ($MgSO_4$), solvents evaporated, the acidic residue (0.046 g) esterified with diazomethane and chromatographed over silica gel. Elution with benzene:ethyl acetate (7:3) gave 0.028 g (7%) (22), mp 120-121°C.

XVII. Reaction of N-Benzoyl Serine Methyl Ester (25) with 4-^{t}Butyl Iodoxybenzene (1): Isolation of Dehydroalanine (26) and Benzamide:

a. Ser-OMe.HCl:

Dry HCl was passed through a suspension of L-serine (5.25 g, 50 mmol) in dry MeOH (40 ml) for 1 h, the resulting

clear solution evaporated *in vacuo*, the residue admixed with dry MeOH (~20 ml), subjected to passage of HCl for additional 0.5 h, solvents evaporated, the residue crystallised from dry MeOH-ether, filtered, washed with dry ether and dried *in vacuo* over KOH to give 6.6 g (85%) of Ser-OMe.HCl, mp 165-166°C (lit.[57] mp 166°C).

ir : ν_{max} (KBr) cm^{-1}: 3200 (very broad, -OH, $-NH_3$), 1740 (ester).

b. Bz-Ser.OMe:

Benzoyl chloride (4.5 ml, 38 mmol) was added, in drops, to an ice cooled and stirred solution of Ser-OMe.HCl (6 g, 38.4 mmol) in saturated $NaHCO_3$ (~300 ml) keeping the medium basic throughout. The reaction mixture was left stirred for 3 h, extracted with ether (3 x 100 ml), dried ($MgSO_4$), solvents evaporated and the residue on crystallisation from PhH:hexane gave (6.85 g (80%) of Bz-Ser-OMe (25), mp 84-85°C (lit.[58] mp 86°C).

c. Reaction of (25) with (1):

A stirred solution of (25) (0.892 g, 4 mmol) in chlorobenzene (20 ml) was admixed with (1) (1.752 g, 6 mmol), held at 140°C for 6 h, cooled, solvents evaporated, the residue triturated with a saturated solution of $NaHCO_3$ (30 ml) for 3 h, extracted with ethyl acetate (3 x 20 ml) the ethyl acetate

extracts combined, dried ($MgSO_4$), solvents evaporated and the residue (1.582 g) chromatographed over silica gel. Elution with hexane gave 0.696 g (45%) of (2) and with benzene 0.445 g (55%) of (26) as a thick liquid.

ir : ν_{max} (neat) cm^{-1}: 3398 (NH), 1710, 1670 (C=O).

nmr : δ ($CDCl_3$), 60 MHz: 3.8 (s, 3 H, $-COOC\underline{H}_3$), 5.9, 6.7 (br, br, 1 H, 1 H, olefine), 7.1-7.9 (m, 5 H, aromatic), 8.4 (br, 1 H, $-N\underline{H}$).

m/z : 205 (M^+), 206 (M^+ + 1), 146 (M^+ - COOMe).

Anal. Calcd. for $C_{11}H_{11}NO_3$ (Mol. wt. 205):

C, 64.39; H, 5.36; N, 6.82%.

Found: C, 64.18; H, 5.24; N, 6.61%.

Further elution with benzene:ethyl acetate (3:7) gave 0.160 g (34%) of benzamide, mp 126°C.

d. Thermolysis of (25) without (1):

A solution of (25) (0.446 g, 2 mmol) in chlorobenzene (10 ml) was held at 140°C for 10 h, cooled, and solvents evaporated to yield 0.446 g (100%) of unchanged (25).

XVIII. Reaction of Bz-Phe-OMe (27) with 4-^{t}Butyl Iodoxybenzene (1): Isolation of Bz-Asp-di-OMe (8):

A stirred solution of (27) (0.283 g, 1 mmol) in chlorobenzene (10 ml) was admixed with (1) (0.438 g, 1.5 mmol),

held at 140-160°C for 8 h, cooled, solvents evaporated, the residue triturated with saturated aq. $NaHCO_3$ (15 ml) for 3.5 h, extracted with ethyl acetate (3 x 15 ml), the ethyl acetate extracts combined, dried ($MgSO_4$), solvents evaporated and the residue (0.532 g) chromatographed over silica gel. Elution with hexane gave 0.316 g (81%) of (2) and with benzene:ethyl acetate (7:3) 0.182 g of unchanged (27).

The bicarbonate extract was cooled, filtered, acidified with 2 N H_2SO_4, saturated with solid NaCl and extracted with ethyl acetate (3 x 20 ml). The ethyl acetate extracts were combined, dried ($MgSO_4$), solvents evaporated, the acidic residue (0.098 g) esterified with diazomethane and chromatographed over silica gel. Elution with benzene:ethyl acetate (1:4) gave 0.035 g (14%) of (8), identical with an authentic sample.[55]

XIX. Reaction of N-Carbobenzoxy Histidine Methyl Ester (28) with 4-^{t}Butyl Iodoxybenzene (1): Isolation of (29) and Benzyl Carbamate (15):

A stirred soluion of (28) (1.06 g, 3.5 mmol) in chlorobenzene (30 ml) was admixed with (1) (1.022 g, 3.5 mmol), refluxed for 7 h, cooled, solvents evaporated and the residue chromatographed over silica gel. Elution with hexane gave 0.580 g (64%) of (2) and with benzene:ethyl acetate (1:1) 0.157 g (30%) of (15), mp 84°C.

Further elution with benzene:ethyl acetate (3:7) gave 0.442 g (38%) of (29) which on crystallisation from ethyl acetate:hexane gave light yellow crystals, mp 175°C.

ir : ν_{max} (KBr) cm^{-1}: 3320 (NH), 1750 (ester), 1725 (CHO), 1695 (amide).

nmr : δ ($CDCl_3$), 60 MHz: 3.12 (m, 2 H, $-CHC\underline{H}_2CH-$), 3.7 (s, 3 H, $COOC\underline{H}_3$), 4.42 (m, 2 H, 2 x$C\underline{H}$), 5.07 (s, 2 H, $OC\underline{H}_2Ph$), 5.6 (br, 2 H, $CON\underline{H}_2$), 6.71 (br, 2 H, 2 x$N\underline{H}$), 7.28 (s, 5 H, aromatic), 8.16 (s, 1 H, $C\underline{H}O$).

m/z : 337 (M^+), 338 (M^+ + 1), 278 (M^+ - COOMe), 246 (M^+ - CH_2Ph), 230 (M^+ - OCH_2Ph).

XX. Reaction of N-Benzoyl Tryptophan Methyl Ester (30) with 4-^{t}Butyl Iodoxybenzene (1): Isolation of N^{α}-Benzoyl-N-formyl-Kynurenine Methyl Ester (31):

A stirred solution of (30) (0.644 g, 2 mmol) in chlorobenzene (8 ml) was admixed with (1) (0.876 g, 3 mmol), refluxed for 4 h, cooled, solvents evaporated under reduced pressure and the residue chromatographed over silica gel. Elution with benzene:ethyl acetate (7:3) gave 0.11 g of unchanged (30) and 0.410 g (70%) of (31) which was crystallised from ethyl acetate:hexane, mp 94-95°C (lit.[59] mp 95°C).

ir : ν_{max} (KBr) cm^{-1}: 3310 (NH), 1750 (-COOMe), 1730 (> C=O).

nmr : δ ($CDCl_3$), 60 MHz: 3.85 (s + d, 5 H, $-COOC\underline{H}_3$, methylene proton), 5.15 (m, 1 H, tert-proton), 7.05-8.05 (m, 9 H, aromatic), 8.65 (br, 2 H, $-N\underline{H}CHO$, $-N\underline{H}COPh$), 11.3 (br, 1 H, $C\underline{H}O$).

m/z : 354 (M^+).

Anal. Calcd. for $C_{19}H_{18}N_2O_5$ (Mol. wt. 354):

C, 64.40; H, 5.08%.

Found: C, 64.58; H, 5.12%.

XXI. <u>Reaction of 4-^{t}Butyl Iodoxybenzene (1) with N-Benzoyl Proline Methyl Ester (32): Isolation of N-Benzoyl Glutamic Acid Dimethyl Ester (33):</u>

A stirred solution of (32) (0.280 g, 1.2 mmol) in chlorobenzene (15 ml) was admixed with (1) (0.438 g, 1.5 mmol) refluxed for 5 h, cooled, solvents evaporated, the residue triturated with a solution of saturated $NaHCO_3$ (30 ml) for 3 h, extracted with ethyl acetate (3 x 20 ml), the ethyl acetate extracts combined, dried over anhydrous $MgSO_4$, solvents evaporated and the residue (0.537 g) chromatographed over silica gel. Elution with hexane gave 0.291 g (75%) of (2) and with benzene:ethyl acetate (4:1) 0.155 g (56%) of unchanged (32).

The $NaHCO_3$ extract was cooled, filtered, acidified with 2 N H_2SO_4, saturated with solid NaCl and extracted with ethyl acetate (3 x 20 ml). The ethyl acetate extracts were combined,

dried ($MgSO_4$), solvents evaporated, the acidic residue (0.050 g) esterified with diazomethane and chromatographed over silica gel. Elution with benzene:ethyl acetate (7:3) gave 0.044 g (14%) of (33) as a pale yellow thick syrup.

ir : ν_{max} (neat) cm^{-1}: 3340 (br, NH), 1660 (C=O).

nmr : δ ($CDCl_3$), 60 MHz: 2.04 (m, 4 H, $-C\underline{H}_2C\underline{H}_2COOMe$), 3.61 (s, 3 H, γ-$COOC\underline{H}_3$), 3.73 (s, 3 H, α-$COOC\underline{H}_3$), 4.82 (m, 1 H, -C$\underline{H}$-), 7.12-7.52 (m, 5 H, aromatic).

m/z : 279 (M^+), 220 (M^+ - COOMe).

XXII. Reaction of Phenyl Alanine Methyl Ester (35) with 4-^{t}Butyl Iodoxybenzene (1): Isolation of (36) and (37):

a. Phe-OMe.HCl:

Thionyl chloride (4.9 ml, 67 mmol), in drops, followed by L-phenyl alanine (9 g, 54.5 mmol) was added to stirred and ice-cooled anhydrous methanol (43.5 ml). The mixture was allowed to attain rt, refluxed for 2 h, the clear solution evaporated and the residue on crystallisation from absolute methanol - dry ether gave 10.5 g (89%) of Phe-OMe.HCl as white needles, mp 159-161°C (lit.[60] mp 160°C).

b. Phe-OMe:

Triethylamine (1.8 ml, 13 mmol) was added, in drops to an ice-cooled and stirred solution of Phe-OMe.HCl (2.15 g,

10 mmol) in dry CH_2Cl_2 (20 ml) left aside for 0.5 h, washed with cold water (2 x 25 ml), dried ($MgSO_4$), solvents evaporated and the resulting Phe-OMe (35) 0.96 g (54%) used as such in the following reaction.

c. Reaction of (35) with (1):

A stirred solution of (35) (0.242 g, 1.3 mmol) in chlorobenzene (15 ml) was admixed with (1) (0.584 g, 2 mmol) refluxed for 5 h, cooled, solvents evaporated *in vacuo* and the residue (0.612 g) chromatographed over silica gel. Elution with hexane gave 0.400 g (77%) of (2) and with benzene:ethyl acetate (9:1) 0.135 g (32%) of (37).

ir : ν_{max} (neat) cm^{-1}: 1740 (ester).

nmr : δ ($CDCl_3$), 60 MHz: 3.76 (s, 3 H, $COOC\underline{H}_3$), 3.8 (s, 3 H, $COOC\underline{H}_3$), 6.87-7.68 (m, 10 H, aromatic).

m/z : 348 (M^+).

Further elution with benzene:ethyl acetate (7:3) gave 0.105 g (25%) of (36).

ir : ν_{max} (neat) cm^{-1}: 3440 (NH), 1730 (br, ester).

nmr : δ ($CDCl_3$), 60 MHz: 3.73 (s, 6 H, 2 x $COOC\underline{H}_3$), 7.2 (m, 10 H, aromatic), 8.2 (br, 1 H, $N\underline{H}$).

m/z : 335 (M^+), 336 (M^+ + 1).

XXIII. Reaction of Tryptophan Methyl Ester (38) with 4-^{t}Butyl Iodoxybenzene (1): Isolation of (39):

a. Trp-OMe.HCl:

To stirred and ice-salt cooled dry MeOH (25 ml) was added, in drops, $SOCl_2$ (1.9 ml, 26 mmol) followed by L-tryptophan (2 g, 12.5 mmol). The reaction mixture was left stirred for 4 h at -5 to $0^{o}C$, then left stirred at rt overnight, concentrated to ~5 ml *in vacuo*, dry ether gradually added until precipitate just appeared, cooled till precipitation was complete, filtered and dried to yield 1.93 g (61%) to Trp-OMe.HCl, mp $213^{o}C$ (lit.[61] mp 213.5-$214^{o}C$).

b. Trp-OMe:

Triethylamine (3.6 ml, 26 mmol) was added, in drops, to a stirred and ice-cooled solution of Trp-OMe.HCl (5 g, 20 mmol) in dry CH_2Cl_2 (70 ml), left aside for 0.5 h, washed with cold water (3 x 15 ml), dried ($MgSO_4$) and evaporated to yield 3.3 g (75%) of Trp-OMe which was used as such for the following experiment.

c. Reaction of (38) with (1):

A stirred solution of (38) (1.09 g, 5 mmol) in dry benzene (30 ml) was admixed with (1) (0.730 g, 2.5 mmol), left stirred for 1.5 h, filtered, washed with benzene (20 ml), solvents

evaporated and the residue (1.32 g) chromatographed on silica gel. Elution with hexane gave 0.460 g (71%) of (2) and with benzene:ethyl acetate (4:1) 0.556 g (61%) of (39) which on crystallization from benzene:hexane gave reddish crystals, mp 197°C.

ir : ν_{max} (KBr) cm^{-1}: 3300 (br, NH), 1670 (br, C=O).

nmr : δ ($CDCl_3$), 60 MHz: 7.08-7.49 (m, 2 H, aromatic), 7.58 (s, 1 H), 7.88-8.18 (m + d, 2 H), 8.78 (m, 1 H, NH).

m/z : 185 (M^+).

XXIV. Reaction of Benzylamine with 4-^{t}Butyl Iodobenzene Dichloride (3): Isolation of Benzaldehyde:

A stirred solution of benzylamine (0.107 g, 1 mmol) in dry benzene (8 ml) was admixed with (3) (0.331 g, 1 mmol), refluxed for 10 h, cooled, filtered, washed with benzene (20 ml), solvents evaporated *in vacuo* and the residue chromatographed over silica gel. Elution with hexane gave 0.163 g (63%) of (2) and with hexane:benzene (3:7) 0.070 g (67%) of benzaldehyde characterised as its 2:4-DNP derivative, mp 238-240°C (lit.[62] mp 241°C).

XXV. Reaction of Cyclohexanone Oxime with 4-^{t}Butyl Iodobenzene Dichloride (3): Isolation of Cyclohexanone:

A solution of (3) (0.331 g, 1 mmol) and cyclohexanone oxime (0.113 g, 1 mmol) in dry benzene (10 ml) was refluxed

for 8 h, cooled, solvents evaporated in vacuo and the residue chromatographed over silica gel. Elution with hexane gave 0.240 g (93%) of (2) and with hexane:benzene (1:1) 0.085 g (87%) of cyclohexanone characterised as its 2:4-DNP derivative, mp 157°C whose ir was identical to that of an authentic derivative (lit.[62] mp 161°C).

XXVI. Reaction of Camphene with 4-^{t}Butyl Iodobenzene Dichloride (3):

A solution of (3) (0.331 g, 1 mmol) and camphene (0.136 g, 1 mmol) in dry benzene (10 ml) was refluxed for 10 h, cooled, solvents evaporated in vacuo and the residue chromatographed on silica gel. Elution with hexane gave 0.190 g (74%) of (2) and with hexane:benzene (4:1) 0.095 g (46%) of a mixture of chlorinated products (tlc, nmr).

XXVII. Preparation of 2-Nitroethyl Phenyl Sulfoxide (41):

a. 2-Bromoethanol:

A mixture of ethylene glycol (60 g, 50 ml, 960 mmol) and HBr (48%, 50 ml) was refluxed for 8 h (bath temp. 140°) concentrated by removal of 50 ml distillate, neutralised with sodium carbonate, saturated with sodium sulfate, extracted with ether, dried ($MgSO_4$), solvents evaporated and the residue on distillation gave 36 g (30%) of 2-bromoethanol, bp 149-150°C (lit.[63] bp 149-150°C).

b. Phenyl 2-hydroxyethyl Sulfide:

A mixture of 2-bromoethanol (63 g, 500 mmol), thiophenol (55 g, 500 mmol) and aqueous NaOH (20%, 120 ml) was refluxed for 1 h, cooled, the oily layer separated, the aqueous layer extracted with chloroform, combined with the oily layer, dried ($MgSO_4$), solvents evaporated and the residue distilled to give 68 g (88%) of phenyl 2-hydroxy ethyl sulfide, bp 135°C/8 torr (lit.[64] bp 141°C/11 torr).

nmr : δ (CCl_4), 60 MHz: 2.93 (t, 2 H, $PhSC\underline{H}_2$), 3.11-3.81 (m, 2 H, $C\underline{H}_2OH$), 7.16 (s, 5 H, aromatic).

c. 2-Bromoethyl Phenyl Sulfide (<u>43</u>):

Phosphorous tribromide (1.7 ml, 10 mmol) was added in drops, over 0.5 h, to a stirred solution of phenyl 2-hydroxy-ethyl sulfide (4.62 g, 30 mmol), left stirred for 1 h, poured on to cold water, extracted with ether, dried ($MgSO_4$), solvents evaporated and the residue on distillation gave 5.50 g (81%) of (<u>43</u>), bp 120-122°C/0.05 torr.

nmr : δ ($CDCl_3$), 60 MHz: 3.2-3.5 (m, 4 H, $SC\underline{H}_2C\underline{H}_2Br$), 7.21 (s, 5 H, aromatic).

d. 2-Nitroethyl Phenyl Sulfide (<u>42</u>):

To a stirred solution of dry sodium nitrite (1.24 g, 18 mmol) in dry DMSO (20 ml) was added, in drops, over 0.5 h, a solution of (<u>43</u>) (0.8 g, 3.6 mmol) in dry DMSO (15 ml). The reaction mixture was left stirred for 5 h at rt, poured on to cold water (40 ml), extracted with ether, dried (Na_2SO_4),

solvents evaporated and the residue (0.715 g) chromatographed over silica gel. Elution with hexane:benzene (7:3) gave 0.480 g (72%) of (42) identical with that of an authentic sample.

ir : ν_{max} (neat) cm^{-1}: 1550, 1370 ($-NO_2$).

nmr : δ ($CDCl_3$), 60 MHz: 3.3 (t, 2 H, $PhSC\underline{H}_2$), 4.37 (t, 2 H, $C\underline{H}_2NO_2$), 7.22 (m, 5 H, aromatic).

e. 2-Nitroethyl Phenyl Sulfoxide (41):

A mixture of (42) (0.183 g, 1 mmol), (1) (0.292 g, 1 mmol), dry benzene (10 ml), and TFA (0.2 ml) was left stirred at rt (~30°C) overnight, filtered, washed with dry benzene, solvents evaporated and the residue (0.195 g) chromatographed on silica gel. Elution with benzene:ethyl acetate (4:1) gave 0.190 g (96%) of (41), mp 64°C identical to that of an authentic sample.[66]

ir : ν_{max} (KBr) cm^{-1}: 1570, 1380 ($-NO_2$), 1045 (SO).

nmr : δ ($CDCl_3$), 60 MHz: 3.43 (m, 2 H, $PhSOC\underline{H}_2$), 4.69 (m, 2 H, $-C\underline{H}_2NO_2$), 7.59 (s, 5 H, aromatic).

XXVIII. Preparation of 2-Chloroethyl Phenyl Sulphide (45):

Thionyl chloride (37.5 g, 23 ml, 315 mmol) was added in drops, over 0.5 h, to a stirred solution of 2-hydroxyethyl phenyl sulfide (28 g, 180 mmol) in dry chloroform (50 ml). The reaction mixture was left stirred for 0.5 h, evaporated and the

residue distilled to give 30 g (96%) of 45), bp 114°C/2 torr (lit.[64] bp 107°C/7 torr).

nmr : δ ($CDCl_3$), 60 MHz: 2.9-3.22 (m, 2 H, $SC\underline{H}_2$), 3.4-3.7 (m, 2 H, $C\underline{H}_2Cl$), 7.2 (s, 5 H, aromatic).

XXIX. Reaction of 2-Bromoethyl Phenyl Sulfide (43) with $AgNO_2$ in Ether: Isolation of (42) and (44):

To stirred silver nitrite (3.08 g, 20 mmol) in dry ether (25 ml) at rt was added, in drops, over 1 h (43) (2.17 g, 10 mmol). The reaction mixture was left stirred for 14 h, filtered, washed with ether, the combined filtrates evaporated and the residue chromatographed over silica gel. Elution with hexane:benzene (3:1) gave 1.15 g (63%) of (42) and 0.35 g (20%) (44).

42: ir : ν_{max} (neat) cm^{-1}: 1550, 1370 ($-NO_2$).

nmr : δ ($CDCl_3$), 60 MHz: 3.3 (t, 2 H, $PhSC\underline{H}_2$), 4.37 (t, 2 H, $C\underline{H}_2NO_2$), 7.22 (m; 5 H, aromatic).

44: ir : ν_{max} (neat) cm^{-1}: 1640, 1280 (ON=O).

nmr : δ ($CDCl_3$), 60 MHz: 3.06 (t, 2 H, $PhSC\underline{H}_2$), 4.45 (t, 2 H, $C\underline{H}_2ON{=}O$), 7.25 (s, 5 H, aromatic).

XXX. Reaction of 2-Chloroethyl Phenyl Sulfide (45) with $AgNO_2$ in Ether: Isolation of (42) and (44):

To a stirred and cooled (~10°) suspension of silver nitrite (1.54 g, 10 mmol) in dry ether (20 ml) was added in drops, (45) (0.86 g, 5 mmol) over 0.5 h. The reaction mixture was left stirred for 38 h at rt, filtered, washed with ether, the combined filtrates evaporated and the residue chromatographed over silica gel. Elution with hexane:benzene (3:1) gave 0.356 g (39%) (42) and 0.530 g (58%) of (44).

XXXI. Reaction of 2-Bromoethyl Phenyl Sulfide (43) with $NaNO_2$ in DMF: Isolation of (42):

To a stirred solution of sodium nitrite (1.24 g, 18 mmol) in dry DMF (20 ml) was added, in drops, over 0.5 h, a solution of (43) (0.8 g, 3.6 mmol) in dry DMF (15 ml). The reaction mixture was left stirred for 24 h at rt, poured on to cold water (40 ml), extracted with ether, dried (Na_2SO_4), solvents evaporated *in vacuo* and the residue (0.548 g) chromatographed on silica gel. Elution with hexane:benzene (7:3) gave 0.416 g (62%) of (42).

XXXII. Attempted Isomerization (44) to (42) in DMSO:

A solution of (44) (0.1 g) in dry DMSO (10 ml) was left stirred overnight at rt; tlc showed no (42) was formed.

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